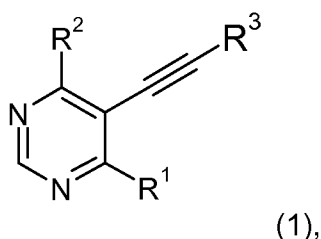


5 - ALKYNYL PYRIMIDINES AND THEIR USE AS KINASE INHIBITORS

The present invention relates to new 5-alkynyl-pyrimidines of general formula (1)



wherein the groups R¹ to R³ have the meanings given in the claims and specification,
the isomers thereof, processes for preparing these alkynyl-pyrimidines and their use as
medicaments.

Background to the invention

A number of protein kinases have already proved to be suitable target molecules for
therapeutic intervention in a variety of indications, e.g. cancer and inflammatory and
autoimmune diseases. Since a high percentage of the genes involved in the development
of cancer which have been identified thus far encode kinases, these enzymes are
attractive target molecules for the therapy of cancer in particular.

Phosphatidylinositol-3-kinases (PI3-kinases) are a subfamily of the lipid kinases which
catalyse the transfer of a phosphate group to the 3'-position of the inositol ring of
phosphoinositides.

The phosphoinositide 3-kinase (PI3K) pathway is activated in a broad spectrum of human
cancers. This may occur either via mutation of PI3K resulting in activation of the kinase,
or indirectly via inactivation of the phosphatase and tensin homologue (PTEN)
suppressor. In both cases, an activation of the signalling cascade is induced that promotes
transformation of cells both in vitro and in vivo. Within the cascade, the PI3K family of
enzymes and the kinase mTOR play a pivotal role. The PI3K family comprises 15 lipid
kinases with distinct substrate specificities, expression pattern and modes of regulation.
They play an important role in numerous cell processes such as e.g. cell growth and

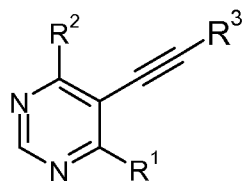
differentiation processes, the control of cytoskeletal changes and the regulation of intracellular transport processes. On the basis of their in vitro specificity for certain phosphoinositide substrates the PI3-kinases can be divided into different categories. The mammalian target of rapamycin (mTOR) is a serine/threonine kinase related to the lipid kinases of the PI3-kinase family. It exists in two complexes, mTORC1 and mTORC2, which are differentially regulated, have distinct substrate specificities, and are differentially sensitive to rapamycin. The central role of mTOR in controlling key cellular growth and survival pathways has sparked interest in 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 PI3K α and mTOR, has emerged as an attractive target for cancer therapeutics. play an important role in numerous cell processes such as e.g. cell growth and differentiation processes, the control of cytoskeletal changes and the regulation of intracellular transport processes. On the basis of their in vitro specificity for certain phosphoinositide substrates the PI3-kinases can be divided into different categories.

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

Detailed description of the invention

It has now surprisingly been found that compounds of general formula (1), wherein the groups R¹ to R⁴ have the meanings given below, act as inhibitors of kinases. In particular the compounds of the invention are useful as inhibitors of PI3K α and mTOR. 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

R³ denotes a group selected from among C₃₋₈cycloalkyl, 3-8 membered heterocycloalkyl, C₆₋₁₀aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different **R⁴**; and

R¹ denotes a group selected from among C₃₋₈cycloalkyl, 3-13 membered heterocycloalkyl, and 2-6 membered heteroalkyl, optionally substituted by one or more identical or different **R⁵** and

R² denotes a group selected from among hydrogen, C₁₋₄alkyl, 3-8 membered heteroalkyl, C₁₋₄haloalkyl, C₃₋₈cycloalkyl, 3-8 membered heterocycloalkyl, -OR^v, -NR^vR^{v'}, -SR^v, -CF₃, -CHF₂, -CH₂F, -CN, -NC and -NO₂, and

each **R⁴** denotes a group selected from among R^a and R^b; and

each **R^a** independently denotes hydrogen or a group selected from among C₁₋₆alkyl, 2-6 membered heteroalkyl, C₁₋₆haloalkyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl, wherein R^a is optionally substituted by one or more identical or different **R^b** and/or **R^{c4}**;

each **R^b** denotes a suitable group and is selected independently of one another from among -OR^{c41}, C₁₋₃haloalkyloxy, -OCF₃, -OCHF₂, -SR^{c41}, -NR^{c41}R^{c42}, -ONR^{c41}R^{c42}, -N(OR^{c41})R^{c42}, -N(R^g)NR^{c41}R^{c42}, halogen, -CF₃, -CHF₂, -CH₂F, -CN, -NC, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, and

each **R⁴**, **R^{c41}** and **R^{c42}** independently of one another denotes hydrogen or a group selected from among C₁₋₆alkyl, 2-6 membered heteroalkyl, C₁₋₆haloalkyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 5-12 membered hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl, wherein **R^{c41}** and **R^{c42}** independently optionally being substituted by one or more identical or different **R^d** and/or **R^{e4}**, and where **R^{c41}** and **R^{c42}** taken

together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N- O- or S-atom, and

each $\mathbf{R}^d$ denotes a suitable group and is selected independently of one another from among $-\text{OR}^{e41}$, C_{1-3} haloalkyloxy, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{SR}^{e41}$, $-\text{NR}^{e41}\text{R}^{e42}$, $-\text{ONR}^{e41}\text{R}^{e42}$,
 5 $-\text{N}(\text{R}^g)\text{NR}^{e41}\text{R}^{e42}$, halogen, $-\text{CF}_3$, $-\text{CN}$, $-\text{NC}$, $-\text{OCN}$, $-\text{SCN}$, $-\text{NO}$, $-\text{NO}_2$, $=\text{N}_2$, $-\text{N}_3$ and each $\mathbf{R}^{e4}$, $\mathbf{R}^{e41}$ and $\mathbf{R}^{e42}$ independently of one another denotes hydrogen or a group selected from among C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered

10 heterocycloalkylalkyl, wherein $\mathbf{R}^{e41}$ and $\mathbf{R}^{e42}$ are optionally independently substituted by one or more identical or different $\mathbf{R}^f$ and/or $\mathbf{R}^{g4}$, and where $\mathbf{R}^{e41}$ and/or $\mathbf{R}^{e42}$ taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N- O- or S-atom and

each $\mathbf{R}^f$ denotes a suitable group and in each case is selected independently of one
 15 another from among $=\text{O}$, $-\text{OR}^{g41}$, C_{1-3} haloalkyloxy, $-\text{OCF}_3$, $-\text{OCHF}_2$, $=\text{S}$, $-\text{SR}^{g41}$, $=\text{NR}^{g41}$, $=\text{NOR}^{g41}$, $=\text{NNR}^{g41}\text{R}^{g42}$, $=\text{NN}(\text{R}^h)\text{C}(\text{O})\text{NR}^{g41}\text{R}^{g42}$, $-\text{NR}^{g41}\text{R}^{g42}$, $-\text{ONR}^{g41}\text{R}^{g42}$,
 $-\text{N}(\text{R}^h)\text{NR}^{g41}\text{R}^{g42}$, halogen, $-\text{CF}_3$, $-\text{CN}$, $-\text{NC}$, $-\text{OCN}$, $-\text{SCN}$, $-\text{NO}$, $-\text{NO}_2$, $=\text{N}_2$, $-\text{N}_3$,
 $-\text{S}(\text{O})\text{R}^{g41}$, $-\text{S}(\text{O})\text{OR}^{g41}$, $-\text{S}(\text{O})_2\text{R}^{g41}$, $-\text{S}(\text{O})_2\text{OR}^{g41}$, $-\text{S}(\text{O})\text{NR}^{g41}\text{R}^{g42}$, $-\text{S}(\text{O})_2\text{NR}^{g41}\text{R}^{g42}$,
 $-\text{OS}(\text{O})\text{R}^{g41}$, $-\text{OS}(\text{O})_2\text{R}^{g41}$, $-\text{OS}(\text{O})_2\text{OR}^{g41}$, $-\text{OS}(\text{O})\text{NR}^{g41}\text{R}^{g42}$, $-\text{OS}(\text{O})_2\text{NR}^{g41}\text{R}^{g42}$,
 20 $-\text{C}(\text{O})\text{R}^{g41}$, $-\text{C}(\text{O})\text{OR}^{g41}$, $-\text{C}(\text{O})\text{SR}^{g41}$, $-\text{C}(\text{O})\text{NR}^{g41}\text{R}^{g42}$, $-\text{C}(\text{O})\text{N}(\text{R}^h)\text{NR}^{g41}\text{R}^{g42}$,
 $-\text{C}(\text{O})\text{N}(\text{R}^h)\text{OR}^{g41}$, $-\text{C}(\text{NR}^h)\text{NR}^{g41}\text{R}^{g42}$, $-\text{C}(\text{NOH})\text{R}^{g41}$, $-\text{C}(\text{NOH})\text{NR}^{g41}\text{R}^{g42}$, $-\text{OC}(\text{O})\text{R}^{g41}$,
 $-\text{OC}(\text{O})\text{OR}^{g41}$, $-\text{OC}(\text{O})\text{SR}^{g41}$, $-\text{OC}(\text{O})\text{NR}^{g41}\text{R}^{g42}$, $-\text{OC}(\text{NR}^h)\text{NR}^{g41}\text{R}^{g42}$, $-\text{SC}(\text{O})\text{R}^{g41}$,
 $-\text{SC}(\text{O})\text{OR}^{g41}$, $-\text{SC}(\text{O})\text{NR}^{g41}\text{R}^{g42}$, $-\text{SC}(\text{NR}^h)\text{NR}^{g41}\text{R}^{g42}$, $-\text{N}(\text{R}^h)\text{C}(\text{O})\text{R}^{g41}$, $-\text{N}[\text{C}(\text{O})\text{R}^{g41}]_2$,
 $-\text{N}(\text{OR}^h)\text{C}(\text{O})\text{R}^{g41}$, $-\text{N}(\text{R}^h)\text{C}(\text{NR}^{h'})\text{R}^{g41}$, $-\text{N}(\text{R}^h)\text{N}(\text{R}^{h'})\text{C}(\text{O})\text{R}^{g41}$, $-\text{N}[\text{C}(\text{O})\text{R}^{g43}]\text{NR}^{g41}\text{R}^{g42}$,
 25 $-\text{N}(\text{R}^h)\text{C}(\text{S})\text{R}^{g41}$, $-\text{N}(\text{R}^h)\text{S}(\text{O})\text{R}^{g41}$, $-\text{N}(\text{R}^h)\text{S}(\text{O})\text{OR}^{g41}$, $-\text{N}(\text{R}^h)\text{S}(\text{O})_2\text{R}^{g41}$,
 $-\text{N}[\text{S}(\text{O})_2\text{R}^{g41}][\text{S}(\text{O})_2\text{R}^{g42}]$, $-\text{N}(\text{R}^h)\text{S}(\text{O})_2\text{OR}^{g41}$, $-\text{N}(\text{R}^h)\text{S}(\text{O})_2\text{NR}^{g41}\text{R}^{g42}$,
 $-\text{N}(\text{R}^h)[\text{S}(\text{O})_2]_2\text{R}^{g41}$, $-\text{N}(\text{R}^h)\text{C}(\text{O})\text{OR}^{g41}$, $-\text{N}(\text{R}^h)\text{C}(\text{O})\text{SR}^{g41}$, $-\text{N}(\text{R}^h)\text{C}(\text{O})\text{NR}^{g41}\text{R}^{g42}$,
 $-\text{N}(\text{R}^h)\text{C}(\text{O})\text{NR}^{h'}\text{NR}^{g41}\text{R}^{g42}$, $-\text{N}(\text{R}^h)\text{N}(\text{R}^{h'})\text{C}(\text{O})\text{NR}^{g41}\text{R}^{g42}$, $-\text{N}(\text{R}^h)\text{C}(\text{S})\text{NR}^{g41}\text{R}^{g42}$,
 $-\text{N}(\text{R}^h)\text{C}(\text{O})[\text{N}(\text{R}^{h'})\text{C}(\text{O})]\text{R}^{g41}$, $-\text{N}(\text{R}^h)[\text{C}(\text{O})]_2\text{R}^{g41}$, $-\text{N}\{[\text{C}(\text{O})]_2\text{R}^{g41}\}\{[\text{C}(\text{O})]_2\text{R}^{g42}\}$,
 30 $-\text{N}(\text{R}^h)[\text{C}(\text{O})]_2\text{OR}^{g41}$, $-\text{N}(\text{R}^h)[\text{C}(\text{O})]_2\text{NR}^{g41}\text{R}^{g42}$, $-\text{N}\{[\text{C}(\text{O})]_2\text{OR}^{g41}\}\{[\text{C}(\text{O})]_2\text{OR}^{g41}\}$,
 $-\text{N}\{[\text{C}(\text{O})]_2\text{NR}^{g41}\text{R}^{g42}\}\{[\text{C}(\text{O})]_2\text{NR}^{g41}\text{R}^{g42}\}$, $-\text{N}(\text{R}^h)\text{C}(\text{O})[\text{N}(\text{R}^{h'})\text{C}(\text{O})]\text{OR}^{g41}$,

$-\text{N}(\text{R}^h)\text{C}(\text{NR}^{h'})\text{OR}^{g41}$, $-\text{N}(\text{R}^h)\text{C}(\text{NOH})\text{R}^{g41}$, $-\text{N}(\text{R}^h)\text{C}(\text{NR}^{h'})\text{SR}^{g41}$,
 $-\text{N}(\text{R}^h)\text{C}(\text{NR}^{h'})\text{NR}^{g41}\text{R}^{g42}$; and $-\text{N}=\text{C}(\text{R}^h)\text{NR}^{g41}\text{R}^{g42}$; and
each R^{g4} , R^{g41} , R^{g42} and R^{g43} independently of one another denotes hydrogen or a group
selected from among C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl,
5 C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered hetero-aryl, 6-18
membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered
heterocycloalkylalkyl, where R^{g41} and/or R^{g42} and/or R^{g43} taken together may form a
3-8 membered heterocyclalkyl residue via a shared C-, N- O- or S-atom, wherein each
 R^{g41} , R^{g42} and R^{g43} is optionally independently substituted by one or more identical or
10 different $\text{R}^{h''}$; and
each R^h , $\text{R}^{h'}$ and $\text{R}^{h''}$ is selected independently of one another from among hydrogen,
 C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl,
 C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl,
3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl, where R^h
15 and $\text{R}^{h'}$ taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-,
N-, O- or S-atom, and
each R^5 denotes a group selected from among R^{a5} and/or R^{b5} ,
each R^{a5} independently of one another denotes hydrogen or a group selected from among
 C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl,
20 C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl,
3-14 membered heterocycloalkyl, and 4-14 membered heterocycloalkylalkyl, wherein R^{a5}
optionally being substituted by one or more identical or different R^{b5} and/or R^{c51} ; and
each R^{b5} denotes a suitable group and is selected independently of one another from
among $=\text{O}$, $-\text{OR}^{c5}$, C_{1-3} haloalkyloxy, $-\text{OCF}_3$, $-\text{OCHF}_2$, $=\text{S}$, $-\text{SR}^{c5}$, $=\text{NR}^{c5}$, $=\text{NOR}^{c5}$,
25 $=\text{NNR}^{c5}\text{R}^{c55}$, $=\text{NN}(\text{R}^{g5})\text{C}(\text{O})\text{NR}^{c5}\text{R}^{c55}$, $-\text{NR}^{c5}\text{R}^{c55}$, $-\text{ONR}^{c5}\text{R}^{c55}$, $-\text{N}(\text{OR}^{c5})\text{R}^{c55}$,
 $-\text{N}(\text{R}^{g5})\text{NR}^{c5}\text{R}^{c55}$, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CN}$, $-\text{NC}$, $-\text{OCN}$, $-\text{SCN}$, $-\text{NO}$, $-\text{NO}_2$,
 $=\text{N}_2$, $-\text{N}_3$, $-\text{S}(\text{O})\text{R}^{c5}$, $-\text{S}(\text{O})\text{OR}^{c5}$, $-\text{S}(\text{O})_2\text{R}^{c5}$, $-\text{S}(\text{O})_2\text{OR}^{c5}$, $-\text{S}(\text{O})\text{NR}^{c5}\text{R}^{c55}$,
 $-\text{S}(\text{O})_2\text{NR}^{c5}\text{R}^{c55}$, $-\text{OS}(\text{O})\text{R}^{c5}$, $-\text{OS}(\text{O})_2\text{R}^{c5}$, $-\text{OS}(\text{O})_2\text{OR}^{c5}$, $-\text{OS}(\text{O})\text{NR}^{c5}\text{R}^{c55}$,
 $-\text{OS}(\text{O})_2\text{NR}^{c5}\text{R}^{c55}$, $-\text{C}(\text{O})\text{R}^{c5}$, $-\text{C}(\text{O})\text{OR}^{c5}$, $-\text{C}(\text{O})\text{SR}^{c5}$, $-\text{C}(\text{O})\text{NR}^{c5}\text{R}^{c55}$,
30 $-\text{C}(\text{O})\text{N}(\text{R}^{g5})\text{NR}^{c5}\text{R}^{c55}$, $-\text{C}(\text{O})\text{N}(\text{R}^{g5})\text{OR}^{c5}$, $-\text{C}(\text{NR}^{g5})\text{NR}^{c5}\text{R}^{c55}$, $-\text{C}(\text{NOH})\text{R}^{c5}$,
 $-\text{C}(\text{NOH})\text{NR}^{c5}\text{R}^{c55}$, $-\text{OC}(\text{O})\text{R}^{c5}$, $-\text{OC}(\text{O})\text{OR}^{c5}$, $-\text{OC}(\text{O})\text{SR}^{c5}$, $-\text{OC}(\text{O})\text{NR}^{c5}\text{R}^{c55}$,

- $-\text{OC}(\text{NR}^{\text{g}5})\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$, $-\text{SC}(\text{O})\text{R}^{\text{c}5}$, $-\text{SC}(\text{O})\text{OR}^{\text{c}5}$, $-\text{SC}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$, $-\text{SC}(\text{NR}^{\text{g}5})\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$,
 $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{R}^{\text{c}5}$, $-\text{N}[\text{C}(\text{O})\text{R}^{\text{c}5}]_2$, $-\text{N}(\text{OR}^{\text{g}5})\text{C}(\text{O})\text{R}^{\text{c}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NR}^{\text{g}5})\text{R}^{\text{c}5}$,
 $-\text{N}(\text{R}^{\text{g}5})\text{N}(\text{R}^{\text{g}55})\text{C}(\text{O})\text{R}^{\text{c}5}$, $-\text{N}[\text{C}(\text{O})\text{R}^{\text{c}5}]\text{NR}^{\text{c}55}\text{R}^{\text{c}555}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{S})\text{R}^{\text{c}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})\text{R}^{\text{c}5}$,
 $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})\text{OR}^{\text{c}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})_2\text{R}^{\text{c}5}$, $-\text{N}[\text{S}(\text{O})_2\text{R}^{\text{c}5}]_2$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})_2\text{OR}^{\text{c}5}$,
5 $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})_2\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$, $-\text{N}(\text{R}^{\text{g}5})[\text{S}(\text{O})_2]_2\text{R}^{\text{c}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{OR}^{\text{c}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{SR}^{\text{c}5}$,
 $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{NR}^{\text{g}55}\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$, $-\text{N}(\text{R}^{\text{g}5})\text{N}(\text{R}^{\text{g}55})\text{C}(\text{O})\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$,
 $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{S})\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})_2\text{R}^{\text{c}5}$, $-\text{N}(\text{R}^{\text{g}5})[\text{C}(\text{O})]_2\text{R}^{\text{c}5}$, $-\text{N}\{[\text{C}(\text{O})]_2\text{R}^{\text{c}5}\}_2$,
 $-\text{N}(\text{R}^{\text{g}5})[\text{C}(\text{O})]_2\text{OR}^{\text{c}5}$, $-\text{N}(\text{R}^{\text{g}5})[\text{C}(\text{O})]_2\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$, $-\text{N}\{[\text{C}(\text{O})]_2\text{OR}^{\text{c}5}\}_2$,
 $-\text{N}\{[\text{C}(\text{O})]_2\text{NR}^{\text{c}5}\text{R}^{\text{c}55}\}_2$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})_2\text{OR}^{\text{c}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NR}^{\text{g}55})\text{OR}^{\text{c}5}$,
10 $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NOH})\text{R}^{\text{c}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NR}^{\text{g}55})\text{SR}^{\text{c}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NR}^{\text{g}55})\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$ and
 $-\text{N}=\text{C}(\text{R}^{\text{g}5})\text{NR}^{\text{c}5}\text{R}^{\text{c}55}$ where $\text{R}^{\text{c}5}$ and/or $\text{R}^{\text{c}55}$ and/or $\text{R}^{\text{c}555}$ taken together may form a 3-8
membered heterocyclalkyl residue via a shared C-, N-, O- or S-atom; and
each $\text{R}^{\text{c}51}$, $\text{R}^{\text{c}5}$, $\text{R}^{\text{c}55}$ and $\text{R}^{\text{c}555}$ independently of one another denotes hydrogen or a group
selected from among C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl,
15 C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered hetero-aryl, 6-18
membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered
heterocycloalkylalkyl, wherein each $\text{R}^{\text{c}51}$, $\text{R}^{\text{c}5}$, $\text{R}^{\text{c}55}$ and/or $\text{R}^{\text{c}555}$ optionally being
independently substituted by one or more identical or different $\text{R}^{\text{d}5}$ and/or $\text{R}^{\text{e}51}$; and
each $\text{R}^{\text{d}5}$ denotes a suitable group and is selected independently of one another from
20 among $=\text{O}$, $-\text{OR}^{\text{e}5}$, C_{1-3} haloalkyloxy, $-\text{OCF}_3$, $-\text{OCHF}_2$, $=\text{S}$, $-\text{SR}^{\text{e}5}$, $=\text{NR}^{\text{e}5}$, $=\text{NOR}^{\text{e}5}$,
 $=\text{NNR}^{\text{e}5}\text{R}^{\text{e}55}$, $=\text{NN}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{ONR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{N}(\text{R}^{\text{g}5})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,
halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CN}$, $-\text{NC}$, $-\text{OCN}$, $-\text{SCN}$, $-\text{NO}$, $-\text{NO}_2$, $=\text{N}_2$, $-\text{N}_3$,
 $-\text{S}(\text{O})\text{R}^{\text{e}5}$, $-\text{S}(\text{O})\text{OR}^{\text{e}5}$, $-\text{S}(\text{O})_2\text{R}^{\text{e}5}$, $-\text{S}(\text{O})_2\text{OR}^{\text{e}5}$, $-\text{S}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{S}(\text{O})_2\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,
 $-\text{OS}(\text{O})\text{R}^{\text{e}5}$, $-\text{OS}(\text{O})_2\text{R}^{\text{e}5}$, $-\text{OS}(\text{O})_2\text{OR}^{\text{e}5}$, $-\text{OS}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{OS}(\text{O})_2\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{C}(\text{O})\text{R}^{\text{e}5}$,
25 $-\text{C}(\text{O})\text{OR}^{\text{e}5}$, $-\text{C}(\text{O})\text{SR}^{\text{e}5}$, $-\text{C}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{g}5})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{g}5})\text{OR}^{\text{e}5}$,
 $-\text{C}(\text{NR}^{\text{g}5})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{C}(\text{NOH})\text{R}^{\text{e}5}$, $-\text{C}(\text{NOH})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{OC}(\text{O})\text{R}^{\text{e}5}$, $-\text{OC}(\text{O})\text{OR}^{\text{e}5}$,
 $-\text{OC}(\text{O})\text{SR}^{\text{e}5}$, $-\text{OC}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{OC}(\text{NR}^{\text{g}5})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{SC}(\text{O})\text{R}^{\text{e}5}$, $-\text{SC}(\text{O})\text{OR}^{\text{e}5}$,
 $-\text{SC}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{SC}(\text{NR}^{\text{g}5})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{R}^{\text{e}5}$, $-\text{N}[\text{C}(\text{O})\text{R}^{\text{e}5}]_2$,
 $-\text{N}(\text{OR}^{\text{g}5})\text{C}(\text{O})\text{R}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NR}^{\text{g}55})\text{R}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{N}(\text{R}^{\text{g}55})\text{C}(\text{O})\text{R}^{\text{e}5}$,
30 $-\text{N}[\text{C}(\text{O})\text{R}^{\text{e}5}]\text{NR}^{\text{e}55}\text{R}^{\text{e}555}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{S})\text{R}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})\text{R}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})\text{OR}^{\text{e}5}$
 $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})_2\text{R}^{\text{e}5}$, $-\text{N}[\text{S}(\text{O})_2\text{R}^{\text{e}5}]_2$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})_2\text{OR}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})_2\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,

- $-N(R^{g5})[S(O)_2]_2R^{e5}$, $-N(R^{g5})C(O)OR^{e5}$, $-N(R^{g5})C(O)SR^{e5}$, $-N(R^{g5})C(O)NR^{e5}R^{e55}$,
 $-N(R^{g5})C(O)NR^{g55}NR^{e5}R^{e55}$, $-N(R^{g5})N(R^{g55})C(O)NR^{e5}R^{e55}$, $-N(R^{g5})C(S)NR^{e5}R^{e55}$,
 $-[N(R^{g5})C(O)]_2R^{e5}$, $-N(R^{g5})[C(O)]_2R^{e5}$, $-N\{[C(O)]_2R^{e5}\}_2$, $-N(R^{g5})[C(O)]_2OR^{e5}$,
 $-N(R^{g5})[C(O)]_2NR^{e5}R^{e55}$, $-N\{[C(O)]_2OR^{e5}\}_2$, $-N\{[C(O)]_2NR^{e5}R^{e55}\}_2$,
5 $-[N(R^{g5})C(O)]_2OR^{e5}$, $-N(R^{g5})C(NR^{g55})OR^{e5}$, $-N(R^{g5})C(NOH)R^{e5}$, $-N(R^{g5})C(NR^{g55})SR^{e5}$,
 $-N(R^{g5})C(NR^{g55})NR^{e5}R^{e55}$ and $-N=C(R^{g5})NR^{e5}R^{e55}$, where R^{e5} and/or R^{e55} and/or R^{e555}
taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N-, O-
or S-atom; and
each R^{e51} , R^{e5} , R^{e55} and R^{e555} independently of one another denotes hydrogen or a group
10 selected from among C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl,
 C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered heteroaryl, 6-18 membered
heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered
heterocycloalkylalkyl wherein each R^{e51} , R^{e5} , R^{e55} and/or R^{e555} optionally being
independently substituted by one or more identical or different R^{f5} and/or R^{g51} ; and
15 each R^{f5} denotes a suitable group and in each case is selected independently of one
another from among $=O$, $-OR^{g52}$, C_{1-3} haloalkyloxy, $-OCF_3$, $-OCHF_2$, $=S$, $-SR^{g52}$,
 $=NR^{g52}$, $=NOR^{g52}$, $=NNR^{g52}R^{g53}$, $=NN(R^{h5})C(O)NR^{g52}R^{g53}$, $-NR^{g52}R^{g53}$, $-ONR^{g52}R^{g53}$,
 $-N(R^{h5})NR^{g52}R^{g53}$, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CN$, $-NC$, $-OCN$, $-SCN$, $-NO$,
 $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^{g52}$, $-S(O)OR^{g52}$, $-S(O)_2R^{g52}$, $-S(O)_2OR^{g52}$, $-S(O)NR^{g52}R^{g53}$,
20 $-S(O)_2NR^{g52}R^{g53}$, $-OS(O)R^{g52}$, $-OS(O)_2R^{g52}$, $-OS(O)_2OR^{g52}$, $-OS(O)NR^{g52}R^{g53}$,
 $-OS(O)_2NR^{g52}R^{g53}$, $-C(O)R^{g52}$, $-C(O)OR^{g52}$, $-C(O)SR^{g52}$, $-C(O)NR^{g52}R^{g53}$,
 $-C(O)N(R^{h5})NR^{g52}R^{g53}$, $-C(O)N(R^{h5})OR^{g52}$, $-C(NR^{h5})NR^{g52}R^{g53}$, $-C(NOH)R^{g52}$,
 $-C(NOH)NR^{g52}R^{g53}$, $-OC(O)R^{g52}$, $-OC(O)OR^{g52}$, $-OC(O)SR^{g52}$, $-OC(O)NR^{g52}R^{g53}$,
 $-OC(NR^{h5})NR^{g52}R^{g53}$, $-SC(O)R^{g52}$, $-SC(O)OR^{g52}$, $-SC(O)NR^{g52}R^{g53}$,
25 $-SC(NR^{h5})NR^{g52}R^{g53}$, $-N(R^{h5})C(O)R^{g52}$, $-N[C(O)R^{g52}]_2$, $-N(OR^{h5})C(O)R^{g52}$,
 $-N(R^{h5})C(NR^{h55})R^{g52}$, $-N(R^{h5})N(R^{h55})C(O)R^{g52}$, $-N[C(O)R^{g52}]NR^{g53}R^{g54}$,
 $-N(R^{h5})C(S)R^{g52}$, $-N(R^{h5})S(O)R^{g52}$, $-N(R^{h5})S(O)OR^{g52}$, $-N(R^{h5})S(O)_2R^{g52}$,
 $-N[S(O)_2R^{g52}]_2$, $-N(R^{h5})S(O)_2OR^{g52}$, $-N(R^{h5})S(O)_2NR^{g52}R^{g53}$, $-N(R^{h5})[S(O)_2]_2R^{g52}$,
 $-N(R^{h5})C(O)OR^{g52}$, $-N(R^{h5})C(O)SR^{g52}$, $-N(R^{h5})C(O)NR^{g52}R^{g53}$,
30 $-N(R^{h5})C(O)NR^{h55}NR^{g52}R^{g53}$, $-N(R^{h5})N(R^{h55})C(O)NR^{g52}R^{g53}$, $-N(R^{h5})C(S)NR^{g52}R^{g53}$,
 $-[N(R^{h5})C(O)]_2R^{g52}$, $-N(R^{h5})[C(O)]_2R^{g52}$, $-N\{[C(O)]_2R^{g52}\}_2$, $-N(R^{h5})[C(O)]_2OR^{g52}$,

- $-N(R^{h5})[C(O)]_2NR^{g52}R^{g53}$, $-N\{[C(O)]_2OR^{g52}\}_2$, $-N\{[C(O)]_2NR^{g52}R^{g53}\}_2$,
 $-[N(R^{h5})C(O)]_2OR^{g52}$, $-N(R^{h5})C(NR^{h55})OR^{g52}$, $-N(R^{h5})C(NOH)R^{g52}$,
 $-N(R^{h5})C(NR^{h55})SR^{g52}$, $-N(R^{h5})C(NR^{h55})NR^{g52}R^{g53}$; and $-N=C(R^{h5})NR^{g52}R^{g53}$; and
each R^{g5} , R^{g51} , R^{g52} , R^{g53} , R^{g54} and R^{g55} independently of one another denotes hydrogen
5 or a group selected from among C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl,
 C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered heteroaryl,
6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered
heterocycloalkylalkyl wherein each R^{g5} , R^{g51} , R^{g52} , R^{g53} , R^{g54} and R^{g55} optionally being
independently substituted by one or more identical or different R^{h51} ; and
10 each R^{h51} , R^{h5} , R^{h55} and R^{h555} is selected independently of one another from among
hydrogen, C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl,
 C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered heteroaryl, 6-18 membered
heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered
heterocycloalkylalkyl; and
15 each R^v and $R^{v'}$ is selected independently of one another from among hydrogen,
 C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl,
optionally in the form of the prodrugs, the tautomers, the racemates, the enantiomers, the
diastereomers, the prodrugs and the mixtures thereof, and optionally the
pharmacologically acceptable salts thereof.
- 20 In a preferred embodiment R^2 denotes a group selected from among hydrogen, C_{1-4} alkyl,
 C_{1-4} haloalkyl, 3-8 membered heteroalkyl, C_{3-8} cycloalkyl, 3-8 membered heterocycloalkyl,
 $-OR^v$, $-NR^vR^{v'}$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CN$, $-NC$ and $-NO_2$; and
each R^v and $R^{v'}$ is selected independently of one another from among hydrogen, C_{1-6}
alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl.
- 25 In another preferred embodiment R^2 denotes $-C_{1-4}$ -alkyl.

In another preferred embodiment R^2 denotes $-CH_3$ or $-C_2H_5$.

In another preferred embodiment R^1 denotes 3-13 membered heterocycloalkyl optionally substituted by one or more identical or different R^5 .

In another preferred embodiment $\mathbf{R}^1$ denotes 3-13 membered heterocycloalkyl comprising at least one nitrogen atom in the ring, wherein $\mathbf{R}^1$ is optionally substituted by one or more identical or different $\mathbf{R}^5$ and wherein $\mathbf{R}^1$ is attached to the pyrimidine ring in formula (1) via a nitrogen atom.

- 5 In another preferred embodiment $\mathbf{R}^1$ denotes piperidine, piperazine, morpholine, pyrrolidine, homopiperazine, homomorpholine, thiomorpholine, 3,9-Diaza-spiro[5.5]undecane, 2,9-Diaza-spiro[5.5]undecane, 2,8-Diaza-spiro[4.5]decane, 1,8-Diaza-spiro[4.5]decane, 3-Aza-spiro[5.5]undecane, 1,5-Dioxa-9-aza-spiro[5.5]undecane, 2-Oxa-9-aza-spiro[5.5]undecane, 3-Oxa-9-aza-spiro[5.5]undecane, 10 8-Aza-spiro[4.5]decane, 2-Oxa-8-aza-spiro[4.5]decane, 1,4-Dioxa-8-aza-spiro[4.5]decane, 3-Aza-spiro[5.6]dodecane, 3,9-Diaza-spiro[5.6]dodecane, 9-Oxa-3-aza-spiro[5.6]dodecane or 1,3,8-Triaza-spiro[4.5]decane, wherein $\mathbf{R}^1$ is optionally substituted by one or more identical or different $\mathbf{R}^5$ and wherein $\mathbf{R}^1$ is attached to the pyrimidine ring in formula (1) via a nitrogen atom.
- 15 In another preferred embodiment $\mathbf{R}^5$ independently of one another denotes a group selected from among $\mathbf{R}^{a5}$ and/or $\mathbf{R}^{b5}$; and each $\mathbf{R}^{a5}$ independently of one another denotes hydrogen or a group selected from among C_{1-4} alkyl, 2-6 membered heteroalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl, 3-14 membered 20 heterocycloalkyl, and 4-14 membered heterocycloalkylalkyl, wherein $\mathbf{R}^{a5}$ optionally being substituted by one or more identical or different $\mathbf{R}^{b5}$ and/or $\mathbf{R}^{c51}$; and each $\mathbf{R}^{b5}$ denotes a suitable group and is selected independently of one another from among $=\text{O}$, $-\text{OR}^{c5}$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $=\text{S}$, $-\text{NR}^{c5}\text{R}^{c55}$, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CN}$, $-\text{S}(\text{O})\text{R}^{c5}$, $-\text{S}(\text{O})_2\text{R}^{c5}$, $-\text{S}(\text{O})_2\text{NR}^{c5}\text{R}^{c55}$, $-\text{C}(\text{O})\text{R}^{c5}$, $-\text{C}(\text{O})\text{NR}^{c5}\text{R}^{c55}$, $-\text{C}(\text{O})\text{N}(\text{R}^{g5})\text{OR}^{c5}$, 25 $-\text{OC}(\text{O})\text{NR}^{c5}\text{R}^{c55}$, $-\text{N}(\text{R}^{g5})\text{C}(\text{O})\text{R}^{c5}$, $-\text{N}(\text{R}^{g5})\text{S}(\text{O})_2\text{R}^{c5}$, $-\text{N}(\text{R}^{g5})\text{C}(\text{O})\text{OR}^{c5}$, $-\text{N}(\text{R}^{g5})\text{C}(\text{O})\text{NR}^{c5}\text{R}^{c55}$, where $\mathbf{R}^{c5}$ and $\mathbf{R}^{c55}$ taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N-, O- or S-atom; and each $\mathbf{R}^{c51}$, $\mathbf{R}^{c5}$ and $\mathbf{R}^{c55}$ independently of one another denotes hydrogen or a group selected from among C_{1-3} alkyl, 2-4 membered heteroalkyl, C_{1-2} haloalkyl, C_{3-7} cycloalkyl, 30 C_{6-10} aryl, 5-10 membered heteroaryl, 6-12 membered heteroarylalkyl, 3-10 membered

heterocycloalkyl and 4-10 membered heterocycloalkylalkyl, wherein R^{e51} , R^{e5} and/or R^{e55} independently optionally being substituted by one or more identical or different R^{d5} and/or R^{e51} ; and

each R^{d5} denotes a suitable group and is selected independently of one another from
 5 among =O, -OH, -OCH₃, -OC₂H₅, -OiPr, -OnPr, -OnBu, -OiBu, -OsecBu, -OtBu, -OCF₃, -OCHF₂, -NR^{e5}R^{e55}, halogen, -CF₃, -CHF₂, -CH₂F, -CN, where R^{e5} and R^{e55} taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N-, O- or S-atom; and

each R^{e51} , R^{e5} and R^{e55} independently of one another denotes hydrogen or a group
 10 selected from among methyl, ethyl, prop-2-yl, prop-1-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, methoxymethyl, ethoxymethyl, methoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, phenyl, benzyl, pyridyl, morpholine, piperidine, pyrrolidine, piperazine, tetrahydrofuryl and tetrahydropyranyl, wherein R^{e51} , R^{e5} and/or R^{e55} independently optionally being substituted by one or more identical or
 15 different R^{f5} and/or R^{g51} ; and

each R^{f5} denotes a suitable group and in each case is selected independently of one another from among =O, -OH, -OCH₃, -OC₂H₅, -OCF₃, -OCHF₂, halogen, -CF₃, -CHF₂, -CN and

each R^{g51} independently of one another denotes hydrogen or a group selected from
 20 among C₁₋₄alkyl, 2-6 membered heteroalkyl, C₃₋₈cycloalkyl, 3-10 membered heterocycloalkyl, C₆₋₁₀aryl and 5-12 membered heteroaryl, wherein R^{g51} optionally being substituted by one or more identical or different R^{h51} ; and

each R^{h51} is selected independently of one another from among hydrogen, C₁₋₄alkyl, 2-4 membered heteroalkyl, C₃₋₈cycloalkyl, C₆₋₁₀aryl, 5-8 membered heteroaryl,
 25 3-10 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl.

In another preferred embodiment R^1 denotes piperidine, piperazine, morpholine, 3,9-Diaza-spiro[5.5]undecane, 2,9-Diaza-spiro[5.5]undecane, 2,8-Diaza-spiro[4.5]decane, 1,8-Diaza-spiro[4.5]decane, 1,4-Dioxa-8-aza-spiro[4.5]decane, 3,9-Diaza-spiro[5.6]dodecane, wherein R^1 is optionally substituted by one or more identical
 30 or different R^5 and wherein R^1 is attached to the pyrimidine ring in formula (1) via a nitrogen atom and each R^5 independently of one another denotes a group selected from

- among R^{a5} and/or R^{b5} ; and
- each R^{a5} independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, methoxymethyl, ethoxymethyl, methoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
- 5 cyclopropylmethyl, phenyl, benzyl, pyridyl, pyrimidinyl, morpholine, piperidine, pyrrolidine, piperazine, tetrahydrofuryl and tetrahydropyranyl, wherein R^{a5} optionally being substituted by one or more identical or different R^{b5} and/or R^{c51} ; and
- each R^{b5} denotes a suitable group and is selected independently of one another from among =O, -OH, -OCH₃, -OC₂H₅, -OCF₃, -OCHF₂, =S, -NR^{c5}R^{c55}, halogen, -CF₃,
- 10 -CHF₂, -CH₂F, -CN, -S(O)₂R^{c5}, -S(O)₂NR^{c5}R^{c55}, -C(O)R^{c5}, -C(O)NR^{c5}R^{c55}, -N(R^{g5})C(O)R^{c5}, -N(R^{g5})S(O)₂R^{c5}, -N(R^{g5})C(O)OR^{c5}, -N(R^{g5})C(O)NR^{c5}R^{c55}, where R^{c5} and R^{c55} taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N-, O- or S-atom; and
- each R^{c51} , R^{c5} and R^{c55} independently of one another denotes hydrogen or a group
- 15 selected from among methyl, ethyl, prop-2-yl, prop-1-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, methoxymethyl, ethoxymethyl, methoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, phenyl, benzyl, morpholine, piperidine, pyrrolidine, piperazine, tetrahydrofuryl, tetrahydropyranyl and 5-6 membered heteroaryl, wherein R^{c51} , R^{c5} and R^{c55} independently optionally being substituted by one or more
- 20 identical or different R^{d5} and/or R^{e51} ; and
- each R^{d5} denotes a suitable group and is selected independently of one another from among =O, -OH, -OCH₃, -OC₂H₅, -OCF₃, -OCHF₂, -NR^{e5}R^{e55}, halogen, -CF₃, -CHF₂, -CH₂F, -CN, where R^{e5} and R^{e55} taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N-, O- or S-atom; and
- 25 each R^{e51} , R^{e5} and R^{e55} independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, methoxymethyl, ethoxymethyl, methoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, phenyl, benzyl, pyridyl, morpholine, piperidine, pyrrolidine, piperazine, tetrahydrofuryl, tetrahydropyranyl; and
- 30 each R^{g5} independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, methoxymethyl,

ethoxymethyl, methoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, phenyl, benzyl, pyridyl, morpholine, piperidine, pyrrolidine, piperazine, tetrahydrofuryl, tetrahydropyranyl.

- In another preferred embodiment $\mathbf{R}^3$ denotes C_{6-10} aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different $\mathbf{R}^4$; and each $\mathbf{R}^4$ denotes a group selected from among $\mathbf{R}^a$ and/or $\mathbf{R}^b$; and each $\mathbf{R}^a$ independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl and cyclopropyl, wherein $\mathbf{R}^a$ is optionally substituted by one or more identical or different $\mathbf{R}^b$ and/or $\mathbf{R}^{c4}$; and
- each $\mathbf{R}^b$ denotes a suitable group and is selected independently of one another from among $-\text{OH}$, $-\text{OCH}_3$, $-\text{OC}_2\text{H}_5$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{NR}^{c41}\text{R}^{c42}$, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CN}$, $-\text{NC}$, and
- each $\mathbf{R}^{c4}$, $\mathbf{R}^{c41}$ and $\mathbf{R}^{c42}$ independently of one another denotes hydrogen or a group optionally substituted by one or more identical or different $\mathbf{R}^d$, selected from among methyl, ethyl, prop-1-yl, prop-2-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, aminoethyl, aminopropyl, hydroxyethyl, methoxyethyl, phenyl and pyridyl wherein $\mathbf{R}^{c4}$, $\mathbf{R}^{c41}$ and/or $\mathbf{R}^{c42}$ independently optionally being substituted by one or more identical or different $\mathbf{R}^d$, and where $\mathbf{R}^{c41}$ and $\mathbf{R}^{c42}$ taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N- O- or S-atom, and
- each $\mathbf{R}^d$ denotes a suitable group and is selected independently of one another from among $-\text{OH}$, $-\text{OCH}_3$, $-\text{OC}_2\text{H}_5$, $-\text{O}i\text{Pr}$, $-\text{O}n\text{Pr}$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{NR}^{e41}\text{R}^{e42}$, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CN}$ and
- each $\mathbf{R}^{e41}$ and $\mathbf{R}^{e42}$ independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-1-yl, prop-2-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, aminoethyl, aminopropyl, hydroxyethyl, methoxyethyl, where $\mathbf{R}^{e41}$ and $\mathbf{R}^{e42}$ taken together may form a 5-6 membered heterocyclalkyl residue via a shared C-, N- O- or S-atom.

- In another preferred embodiment $\mathbf{R}^3$ denotes C_{6-10} aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different $\mathbf{R}^4$; and each $\mathbf{R}^4$ denotes a

group selected from among R^a and R^b ; and
each R^a independently of one another denotes hydrogen or a group selected from among
methyl, ethyl, prop-2-yl, prop-1-yl, cyclopropyl, and
each R^b denotes a suitable group and is selected independently of one another from
5 among $-OH$, $-OCH_3$, $-OC_2H_5$, $-OCF_3$, $-OCHF_2$, $-NH_2$, $NHCH_3$, NHC_2H_5 , halogen, $-CF_3$,
 $-CHF_2$, $-CH_2F$, $-CN$.

In another preferred embodiment R^3 denotes phenyl and pyridyl optionally substituted by
one or more identical or different R^4 ; and each R^4 denotes a group selected from among
methyl, ethyl, $-NH_2$, $NHCH_3$, NHC_2H_5 .

10 In a more preferred embodiment R^3 denotes pyridyl, optionally substituted by one or
more identical or different R^4 .

In a further preferred embodiment, R^3 denotes pyridyl, substituted by one or more identical
or different R^4 , preferably each R^4 denotes a group selected from among methyl, ethyl, $-$
 NH_2 , $NHCH_3$, NHC_2H_5 .

15 The present invention also relates to the use of the compounds, or the pharmacologically
effective salts thereof, according to the present invention, as medicaments.

The present invention also relates to the use of the compounds, or the pharmacologically
effective salts thereof, according to the present invention, for preparing a medicament
with an antiproliferative activity.

20 The present invention also relates to pharmaceutical preparations, containing as active
substance one or more compounds of general formula (1) according to the present
invention or the pharmacologically effective salts thereof, optionally in combination with
conventional excipients and/or carriers.

The present invention also relates to compounds according to formula (1) for use in the
25 treatment and/or prevention of cancer, infections, inflammatory and autoimmune
diseases.

The present invention also relates to the use of compounds of general formula (1) according to the present invention for preparing a medicament for the treatment and/or prevention of cancer, infections, inflammatory and autoimmune diseases.

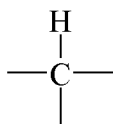
The present invention also relates to pharmaceutical preparations comprising a compound
 5 of general formula (1) according to the present invention and at least one other cytostatic or cytotoxic active substance, different from formula (1), optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, as well as optionally the pharmacologically acceptable salts thereof.

Definitions

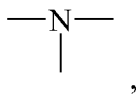
10 As used herein the following definitions apply, unless stated otherwise.

By **alkyl** substituents are meant in each case saturated, unsaturated, straight-chain or branched aliphatic hydrocarbon groups (alkyl group) and this includes both saturated alkyl groups and unsaturated alkenyl and alkynyl groups. Alkenyl substituents are in each case straight-chain or branched, unsaturated alkyl groups, which have at least one double
 15 bond. By alkynyl substituents are meant in each case straight-chain or branched, unsaturated alkyl groups, which have at least one triple bond.

The term **heteroalkyl** refers to groups which can be derived from alkyl as defined above in its broadest sense by replacing one or more of the groups $-\text{CH}_3$ in the hydrocarbon chains independently of one another by the groups $-\text{OH}$, $-\text{SH}$ or $-\text{NH}_2$, one or more of
 20 the groups $-\text{CH}_2-$ independently of one another by the groups $-\text{O}-$, $-\text{S}-$ or $-\text{NH}-$, one or more of the groups



by the group



one or more of the groups =CH– by the group =N–, one or more of the groups =CH₂ by the group =NH or one or more of the groups ≡CH by the group ≡N, while in all only a maximum of three heteroatoms may be present in a heteroalkyl, there must be at least one
 5 carbon atom between two oxygen and between two sulphur atoms or between one oxygen and one sulphur atom and the group as a whole must have chemical stability.

It flows from the indirect definition/derivation from alkyl that heteroalkyl is made up of the sub-groups of saturated hydrocarbon chains with hetero-atom(s), heteroalkenyl and heteroalkynyl, while further subdivision into straight-chain (unbranched) and branched
 10 may be carried out. If a heteroalkyl is supposed to be substituted, the substitution may take place independently of one another, in each case mono- or polysubstituted, at all the hydrogen-carrying oxygen, sulphur, nitrogen and/or carbon atoms. Heteroalkyl itself may be linked to the molecule as substituent both through a carbon atom and through a heteroatom.

15 By way of example, the following representative compounds are listed:
 dimethylaminomethyl; dimethylaminoethyl (1-dimethylaminoethyl; 2-dimethylaminoethyl); dimethylaminopropyl (1-dimethylaminopropyl, 2-dimethylaminopropyl, 3-dimethylaminopropyl); diethylaminomethyl; diethylaminoethyl (1-diethylaminoethyl, 2-diethylaminoethyl); diethylaminopropyl (1-diethylaminopropyl, 2-diethylamino-
 20 propyl, 3-diethylaminopropyl); diisopropylaminoethyl (1-diisopropylaminoethyl, 2-di-isopropylaminoethyl); bis-2-methoxyethylamino; [2-(dimethylamino-ethyl)-ethyl-amino]-methyl; 3-[2-(dimethylamino-ethyl)-ethyl-amino]-propyl; hydroxymethyl; 2-hydroxy-ethyl; 3-hydroxypropyl; methoxy; ethoxy; propoxy; methoxymethyl; 2-methoxyethyl etc.

25 **Haloalkyl** relates to alkyl groups, wherein one or more hydrogen atoms are replaced by halogen atoms. Haloalkyl includes both saturated alkyl groups and unsaturated alkenyl and alkynyl groups, such as for example -CF₃, -CHF₂, -CH₂F, -CF₂CF₃, -CHF₂CF₃, -CH₂CF₃,

-CF₂CH₃, -CHFCH₃, -CF₂CF₂CF₃, -CF₂CH₂CH₃, -CF=CF₂, -CCl=CH₂, -CBr=CH₂,
-CI=CH₂, -C≡C-CF₃, -CHFCH₂CH₃ and -CHFCH₂CF₃.

Halogen refers to fluorine, chlorine, bromine and/or iodine atoms.

C₁₋₃haloalkoxy is meant to be C₁₋₃haloalkyl-O-.

5 By **cycloalkyl** is meant a mono or bicyclic ring or spirocyclic ring, while the ring system may be a saturated ring or, however, an unsaturated, non-aromatic ring, which may optionally also contain double bonds, such as for example cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, norbornyl and norbornenyl.

10 **Cycloalkylalkyl** includes a non-cyclic alkyl group wherein a hydrogen atom bound to a carbon atom, usually to a terminal C atom, is replaced by a cycloalkyl group.

Aryl relates to monocyclic or bicyclic aromatic rings with 6 – 10 carbon atoms such as phenyl and naphthyl, for example.

15 **Arylalkyl** includes a non-cyclic alkyl group wherein a hydrogen atom bound to a carbon atom, usually to a terminal C atom, is replaced by an aryl group.

By **heteroaryl** are meant mono- or bicyclic aromatic rings, which instead of one or more carbon atoms contain one or more, identical or different hetero atoms, such as e.g. nitrogen, sulphur or oxygen atoms. Examples include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, 20 thiadiazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl and triazinyl. Examples of bicyclic heteroaryl groups are indolyl, isoindolyl, benzofuryl, benzothienyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzopyrazolyl, indazolyl, isoquinoliny, quinoliny, quinoxaliny, cinnoliny, phthalazinyl, quinazolinyl and benzotriazinyl, indoliziny, oxazolopyridyl, 25 imidazopyridyl, naphthyridinyl, indoliny, isochromanyl, chromanyl, tetrahydroisoquinoliny, isoindoliny, isobenzotetrahydrofuryl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridyl, benztetrahydrofuryl,

benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridyl-*N*-oxide

5 tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl-*N*-oxide, pyrimidinyl-*N*-oxide, pyridazinyl-*N*-oxide, pyrazinyl-*N*-oxide, quinolinyl-*N*-oxide, indolyl-*N*-oxide, indolinyl-*N*-oxide, isoquinolyl-*N*-oxide, quinazolinyl-*N*-oxide, quinoxalinyl-*N*-oxide, phthalazinyl-*N*-oxide, imidazolyl-

10 *N*-oxide, isoxazolyl-*N*-oxide, oxazolyl-*N*-oxide, thiazolyl-*N*-oxide, indolizinyll-*N*-oxide, indazolyl-*N*-oxide, benzothiazolyl-*N*-oxide, benzimidazolyl-*N*-oxide, pyrrolyl-*N*-oxide, oxadiazolyl-*N*-oxide, thiadiazolyl-*N*-oxide, triazolyl-*N*-oxide, tetrazolyl-*N*-oxide, benzothiopyranyl-*S*-oxide and benzothiopyranyl-*S,S*-dioxide.

Heteroarylalkyl encompasses a non-cyclic alkyl group wherein a hydrogen atom bound

15 to a carbon atom, usually to a terminal C atom, is replaced by a heteroaryl group.

Heterocyloalkyl relates to saturated or unsaturated, non-aromatic mono-, bicyclic, bridged bicyclic or spirocyclic rings comprising 3 – 13 carbon atoms, which instead of one or more carbon atoms carry heteroatoms, such as nitrogen, oxygen or sulphur. Examples of such heterocyloalkyl groups are tetrahydrofuryl, pyrrolidinyl, pyrrolinyl,

20 imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, indolinyl, isoindolinyl, morpholinyl, thiomorpholinyl, homomorpholinyl, homopiperidinyl, homopiperazinyl, homothiomorpholinyl, thiomorpholinyl-*S*-oxide, thiomorpholinyl-*S,S*-dioxide, tetrahydropyranyl, tetrahydrothienyl, homothiomorpholinyl-*S,S*-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl,

25 dihydropyrazinyl, dihydropyridyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl-*S*-oxide, tetrahydrothienyl-*S,S*-dioxide, homothiomorpholinyl-*S*-oxide, 2-oxa-5-azabicyclo[2,2,1]heptane, 8-oxa-3-aza-bicyclo[3.2.1]octane, 3,8-diaza-bicyclo[3.2.1]octane, 2,5-diaza-bicyclo[2.2.1]heptane, 3,8-diaza-bicyclo[3.2.1]octane, 3,9-diaza-bicyclo[4.2.1]nonane, 2,6-diaza-

30 bicyclo[3.2.2]nonane, 3,9-Diaza-spiro[5.5]undecane, 2,9-Diaza-spiro[5.5]undecane,

2,8-Diaza-spiro[4.5]decane, 1,8-Diaza-spiro[4.5]decane, 3-Aza-spiro[5.5]undecane, 1,5-Dioxa-9-aza-spiro[5.5]undecane, 2-Oxa-9-aza-spiro[5.5]undecane, 3-Oxa-9-aza-spiro[5.5]undecane, 8-Aza-spiro[4.5]decane, 2-Oxa-8-aza-spiro[4.5]decane, 1,4-Dioxa-8-aza-spiro[4.5]decane, 3-Aza-spiro[5.6]dodecane, 3,9-Diaza-spiro[5.6]dodecane, 9-Oxa-3-aza-spiro[5.6]dodecane and 1,3,8-Triaza-spiro[4.5]decane.

Heterocycloalkylalkyl relates to a non-cyclic alkyl group wherein a hydrogen atom bound to a carbon atom, usually to a terminal C atom, is replaced by a heterocycloalkyl group.

The following Examples illustrate the present invention without restricting its scope.

10 **General Procedure 1 (GP1): Iodination of Pyrimidines or Pyridines**

A solution of the pyrimidine or pyridine (1.0 eq.) in acetic acid is cooled to 0 °C and NIS (1.0 eq.) is added in one portion. The reaction mixture is stirred at RT until conversion of the starting material is completed (2 - 6 h). The mixture is poured on ice-cooled water and treated with a mixture of 5 % Na₂S₂O₃ and 10 % NaHCO₃. The precipitate is filtered off, intensely washed with water and dried under vacuum at 40°C. The crude product can be used without further purification or is further purified by chromatography on silica gel using a CH₂Cl₂/MeOH gradient.

General Procedure 2 (GP2): Sonogashira Reaction

Method 1:

20 The halide (1.0 eq.) is dissolved in DMF or THF and 0.1 eq. Pd-catalyst (e.g. PdCl₂(PPh₃)₂ or Pd(PPh₃)₄) and CuI (0.1 eq.) are added. Subsequently, triethylamine (10.0 eq.) and finally the alkyne (1.5 eq.) are added and the reaction mixture is stirred at 65 °C. The reaction is monitored by LC-MS. If the iodide is not completely converted after 4 h, additional amounts of alkyne are added in small portions. The product either precipitates from the reaction mixture (and is filtered off and if necessary re-crystallized) and/or, after removal of the solvent, is purified by preparative RP-HPLC or chromatography on silica gel.

Method 2:

The halide (1.0 eq.) is dissolved in DMSO and Pd(PPh₃)₄ (0.1 eq.) and CuI (0.1 eq.) are added. Subsequently, diisopropylamine (0.9 eq.) and finally the alkyne (1.2 eq.) are added. The reaction mixture is put on a pre-heated hot plate and stirred at 80 °C. The
5 reaction is monitored by LC-MS. If the halide is not completely converted after 4 h, additional amounts of alkyne are added in small portions. The product either precipitates from the reaction mixture (and is filtered off and if necessary re-crystallized) and/or, after removal of the solvent, is purified by preparative RP-HPLC or flash chromatography on silica gel.

10 General Procedure 3 (GP3): Desilylation of Alkynes

The TMS-alkyne (1.0 eq.) is dissolved in MeOH, K₂CO₃ (0.5 eq.) is added in one portion and the reaction mixture is stirred at RT until conversion is complete (3 – 16 h). The solvent is removed *in vacuo*, the crude product is dissolved in ethyl acetate and the organic phase is extracted with water. The organic phase is dried, filtered off and the
15 solvent removed *in vacuo*. The product is either used without further purification or purified by chromatography on silica gel using a DCM/MeOH or (cyclo-)hexane/ethyl acetate.

General Procedure 5 (GP5): Oxidation of a Thioalkyl Group

The 2-methylsulfanyl-pyrimidine (1.0 eq.) is taken up in DCM, *meta*-chloroperoxybenzoic
20 acid (2.5 eq.) is added and the reaction mixture is stirred for one day. The reaction mixture is filtered, washed with water and concentrated *in vacuo*. The crude product can be used without further purification.

General Procedure 6 (GP6):**Nucleophilic Substitution of 2-Sulfonylpyrimidines with Amines**

25 The starting material is dissolved in NMP, an excess of amine is added and the reaction mixture is heated in the microwave at 120-150 °C. After cooling to RT the product is purified by NP-HPLC.

General Procedure 7 (GP7):**Nucleophilic Substitution of 4-Chloropyrimidines with Amines**Method 1:

The starting material is dissolved in NMP, an excess of amine is added and the reaction
5 mixture is heated in the microwave at 120 - 150°C. After cooling to RT the product is
purified by NP-HPLC.

Method 2:

To a mixture of starting material in acetonitril is added DIPEA. The reaction mixture is
stirred for 1 – 12 h at RT or 80°C. After cooling to RT the product is either purified by
10 prep. HPLC (NP or RP) or the solvent is removed under reduced pressure, the residue is
taken up in DCM (with a little MeOH if necessary) and filtered over silica. After removal
of the solvent the residue is taken up in water and DCM and the aqueous phase is
extracted twice with DCM. The combined organic layers are dried over MgSO₄ and the
solvent is removed under reduced pressure yielding the desired product. If necessary the
15 product is recrystallized from ACN.

General Procedure 8 (GP8): Saponification of Esters

The ester is taken up in either THF or dioxane, 1.1-1.5 eq. of 1 N NaOH are added and
the mixture is heated under reflux until reaction control shows complete conversion of the
starting material. The product either precipitates from the reaction mixture and is used
20 without additional purification steps or can further be purified by chromatography.

General Procedure 9 (GP9): Amide Formation with Amines

A mixture of 0.21 mmol starting material, 0.31 mmol TBTU or HATU and 0.42 mmol
Huenig's base in 2 mL DMSO is stirred for 5 min. Subsequently 0.31 mmol of amine is
added and the resultant mixture is stirred at RT over night. Purification is performed via
25 preparative RP-HPLC yielding after evaporation of the solvent the desired product.

General Procedure 10 (GP10) Amide Formation with Acid Chlorides

To a mixture of 0.13 mmol of starting material and 67 µL Huenig's base in 2 mL THF is
added 0.26 mmol acid chloride. The reaction mixture is stirred over night at RT. The
solvent is evaporated and the residue is taken up in 1 mL DMSO. Insoluble material is

filtered off and the resulting solution is purified via preparative RP-HPLC yielding after evaporation of the solvent the desired product.

General Procedure 11 (GP11): Urea Formation with Isocyanates

To a mixture of 0.16 mmol of starting material and 64.4 μ L Huenig's base in 2 mL THF is added 0.49 mmol isocyanate. The reaction mixture is stirred over night at RT. The solvent is evaporated and the residue is taken up in 1 mL DMSO. Insoluble material is filtered off and the resulting solution is purified via preparative RP-HPLC yielding after evaporation of the solvent the desired product.

General Procedure 12 (GP12): Urea Formation via Pre-activation of the Amine

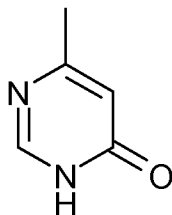
A mixture of 0.34 mmol amine and 0.34 mmol *N,N'*-carbonyldiimidazole and 0.34 mmol 1,8-diazabicyclo[5.4.0]undec-7-ene is stirred for 10 min at RT. Then 0.32 mmol of starting material is added in one portion. The reaction mixture is heated at 100 °C for 1 h in the microwave. The solvent is evaporated and the residue is taken up in 1 mL DMSO. Insoluble material is filtered off and the resulting solution is purified via preparative RP-HPLC yielding the desired product.

General Procedure 13 (GP13): Amide formation with carbonic acids

A mixture of 0.62 mmol carbonic acid, 0.93 mmol TBTU and 1.2 mmol Huenig's base in 2 mL DMSO is stirred for 5 min. Subsequently 0.31 mmol of starting material is added and the resultant mixture is stirred at RT over night. Purification is performed via preparative RP-HPLC yielding after evaporation of the solvent the desired product.

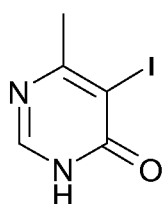
Intermediates A

A-1a) 6-Methyl-3H-pyrimidin-4-one



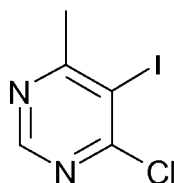
100 g (0.70 mol) 4-Hydroxy-2-mercapto-6-methyl pyrimidine and 300 g Raney-Nickel are suspended in water (1000 mL) and the suspension is heated and stirred under reflux over night. Full conversion is detected by TLC (10 % MeOH in DCM). The catalyst is filtered off over celite and the filtrate is evaporated to give crude product as a pale green solid. The product is used without further purification for the next step.

A-1b) 5-Iodo-6-methyl-3H-pyrimidin-4-one

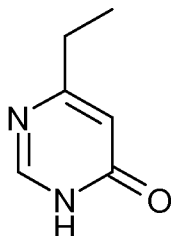


To a stirred solution of 70 g (0.64 mol) 4-hydroxy-6-methyl pyrimidine in acetic acid is added 127 g (0.56 mol) NIS portion wise at RT within 15 min. The reaction is stirred for 30 h at RT until all starting material is consumed. The reaction mixture is diluted with water and the solid product is filtered off and washed with sodium thiosulfate solution to remove excess iodine. After drying, the desired product is obtained as a pale brown solid (90 g; 60 %) which is used without further purification.

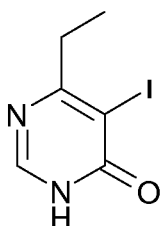
A-1) 4-Chloro-5-iodo-6-methyl-pyrimidin



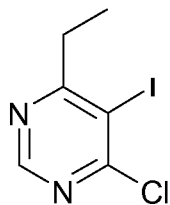
A suspension of 90 g (0.38 mol) 4-hydroxy-5-iodo-6-methyl pyrimidine in 600 mL POCl₃ is heated for 1 h at 90 °C. The reaction mixture is concentrated under reduced pressure and the residue is poured into crushed ice. The precipitated solid is collected by filtration and washed with water. After drying, the desired product is obtained as a solid (90 g; 93 %).

A-2a) 6-Ethyl-3H-pyrimidin-4-one

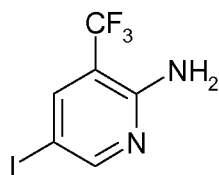
90 g (0.58 mol) 4-Hydroxy-2-mercapto-6-ethyl pyrimidine and 270 g Raney-Nickel are suspended in water (1000 mL). The suspension is heated and stirred under reflux over
5 night. Full conversion is detected by TLC (10 % MeOH in DCM). The catalyst is filtered off over celite and the filtrate is evaporated to give crude product as a pale green solid (70.0 g; 98 %). The product is used without further purification for the next step.

A-2b) 6-Ethyl-5-iodo-3H-pyrimidin-4-one

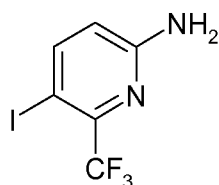
10 To a stirred solution of 70 g (0.56 mol) 4-hydroxy-6-ethyl pyrimidine in acetic acid is added 127 g (0.56 mol) NIS portion wise at RT within 15 min. The reaction is stirred for 30 h at RT until all starting material is consumed. The reaction mixture is diluted with water and the solid product is filtered off and washed with sodium thiosulfate solution to remove excess iodine. After drying, the desired product is obtained as a solid (90 g; 64
15 %) which is used without further purification.

A-2c) 4-Chloro-5-iodo-6-ethyl-pyrimidin

A suspension of 90 g (0.36 mol) 4-hydroxy-5-iodo-6-ethyl pyrimidine in 600 mL POCl₃ is heated for 1 h at 90°C. The reaction mixture is concentrated under reduced pressure and the residue is poured into crushed ice. The precipitated solid is collected by filtration and washed with water. After drying, the desired product is obtained as a solid (65 g; 67 %).

A-2) 5-Iodo-3-trifluoromethyl-pyridin-2-ylamine

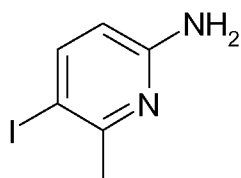
The title compound is synthesized according to general procedure GP1 starting from 5.0 g (31 mmol) 3-trifluoro-pyridin-2-ylamine and 6.9 g (31 mmol) NIS. Yield after precipitation from the reaction mixture: 6.78 g (76 %).

A-3) 6-Trifluoromethyl-5-iodo-pyridin-2-ylamine

The title compound is synthesized according to general procedure GP1 starting from 4.8 g (30 mmol) 6-trifluoromethyl-pyridin-2-ylamine and 6.7 g (30 mmol) NIS. Yield

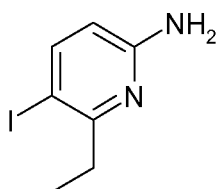
after precipitation from the reaction mixture and isolation of additional product from the mother liquid by chromatography in silica gel: 5.73 g (67 %).

A-4) 5-Iodo-6-methyl-pyridin-2-ylamine



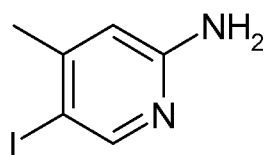
- 5 The title compound is synthesized according to general procedure GP1 starting from 2.7 g (25 mmol) 6-methyl-pyridin-2-ylamine and 5.6 g (25 mmol) NIS. Small amounts of the corresponding bis-iodopyridine are formed during the reaction (LC-MS). The reaction mixture is poured into ice upon which the bis-iodo product precipitated. The mother liquid is treated with a mixture of 5 % Na₂S₂O₃ and 10 % NaHCO₃ and is
- 10 subsequently neutralized by addition of 4 N NaOH. The precipitated product is collected by filtration and washed with water. Yield: 4.95 g (85 %).

A-5) 6-Ethyl-5-iodo-pyridin-2-ylamine



- The title compound is synthesized according to general procedure GP1 starting from
- 15 10.0 g (83 mmol) 6-ethyl-pyridin-2-ylamine and 18.4 g (83 mmol) NIS. Yield after precipitation from the reaction mixture: 18.0 g (89 %).

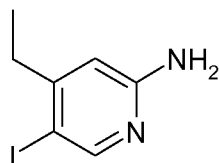
A-6) 5-Iodo-4-methyl-pyridin-2-ylamine



The title compound is synthesized according to general procedure GP1 starting from 2.0 g (18 mmol) 4-methyl-pyridin-2-ylamine and 4.2 g (18 mmol) NIS. Yield after precipitation from the reaction mixture: 3.6 g (83 %).

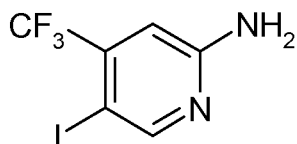
A-7) 4-Ethyl-5-iodo-pyridin-2-ylamine

5



The title compound is synthesized according to general procedure GP1 starting from 5.0 g (41 mmol) 4-ethyl-pyridin-2-ylamine and 9.2 g (41 mmol) NIS. Yield after precipitation from the reaction mixture and isolation of additional product from the mother liquid by chromatography using silica gel: 10.3 g (100 %).

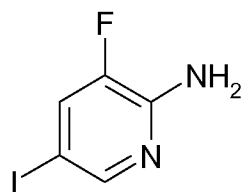
10 **A-8) 4-Trifluoromethyl-5-iodo-pyridin-2-ylamine**



The title compound is synthesized according to general procedure GP1 starting from 20.0 g (123 mmol) 4-trifluoromethyl-pyridin-2-ylamine and 27.8 g (123 mmol) NIS. Yield after precipitation from the reaction mixture and isolation of additional product from the mother liquid by chromatography in silica gel: 20.3 g (57 %).

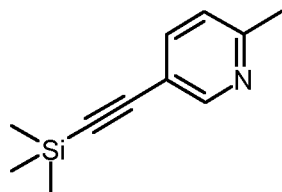
15

A-9) 3-Fluoro-5-iodo-pyridin-2-ylamine



The title compound is synthesized according to general procedure GP1 starting from 200 mg (1.78 mmol) 3-fluoro-pyridin-2-ylamine and 401 mg (1.78 mmol) NIS. Yield after precipitation from the reaction mixture: 380 mg (90 %).

A-10) 2-Methyl-5-trimethylsilanylethynyl-pyridine

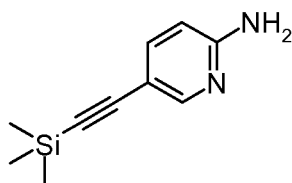


5

The title compound is synthesized according to general procedure GP2 starting from 2.0 g (11.6 mmol) 5-bromo-pyridin-2-ylamine and 2.3 mL (16.3 mmol) 1-trimethylsilyl-ethyne using 68 mg (0.36 mmol) CuI, 305 mg (1.2 mmol) triphenylphosphine, 213 mg (0.30 mmol) PdCl₂(PPh₃)₂ and 18 mL (127 mmol) triethylamine in 18 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using a hexane/ethyl acetate gradient. Yield: 1.5 g (68 %).

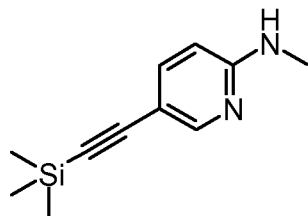
10

A-11) 5-Trimethylsilanylethynyl-pyridin-2-ylamine

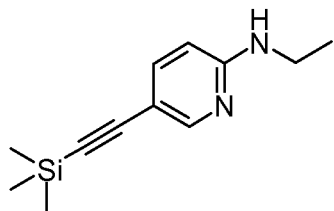


The title compound is synthesized according to general procedure GP2 starting from 5.0 g (28.9 mmol) 5-bromo-pyridin-2-ylamine and 5.7 mL (40.5 mmol) 1-trimethylsilyl-ethyne using 168 mg (0.88 mmol) CuI, 758 mg (2.9 mmol) triphenylphosphine, 533 mg (0.76 mmol) PdCl₂(PPh₃)₂ and 40 mL (288 mmol) triethylamine in 40 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate and small amounts of cyclohexane, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using hexane/ethyl acetate (10/1 v/v). Yield: 5.0 g (91 %).

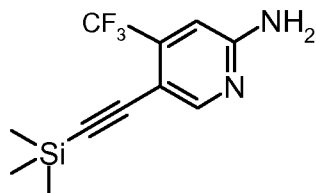
20

A-12) Methyl-(5-trimethylsilanylethynyl-pyridin-2-yl)-amine

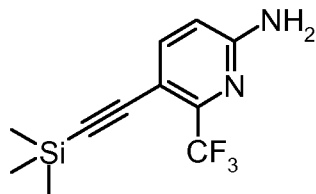
The title compound is synthesized according to general procedure GP2 starting from 4.3 g (23.0 mmol) 5-bromo-2-methylamino-pyridine and 4.5 mL (32.2 mmol) 1-trimethylsilyl-ethyne using 134 mg (0.71 mmol) CuI, 601 mg (2.3 mmol) triphenylphosphine, 420 mg (0.60 mmol) PdCl₂(PPh₃)₂ and 32 mL (101 mmol) triethylamine in 40 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate and small amounts of cyclohexane, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using a hexane/ethyl acetate gradient. Yield: 4.0 g (85 %).

A-13) Ethyl-(5-trimethylsilanylethynyl-pyridin-2-yl)-amine

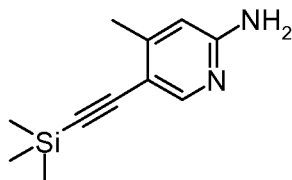
The title compound is synthesized according to general procedure GP2 starting from 909 mg (4.5 mmol) 5-bromo-2-ethylamino-pyridine and 0.89 mL (6.3 mmol) 1-trimethylsilyl-ethyne using 26 mg (0.13 mmol) CuI, 118 mg (0.45 mmol) triphenylphosphine, 82 mg (0.12 mmol) PdCl₂(PPh₃)₂ and 6.3 mL (45.0 mmol) triethylamine in 7 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate and small amounts of cyclohexane, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using a hexane/ethyl acetate gradient. Yield: 980 mg (99 %).

A-14) 4-Trifluoromethyl-5-trimethylsilanylethynyl-pyridin-2-ylamine

The title compound is synthesized according to general procedure GP2 starting from 12.8 g (44 mmol) 4-trifluoromethyl-5-iodo-pyridin-2-ylamine and 8.8 mL (62 mmol) 1-trimethyl-silyl-ethyne using 844 mg (4.4 mmol) CuI, 3.1 g (4.4 mmol) PdCl₂(PPh₃)₂ and 62 mL (443 mmol) triethylamine in 80 mL dry THF. For the work-up the solvent is removed under reduced pressure, the crude product is taken up in ethyl acetate and the organic phase is extracted with water. The product is purified twice by chromatography on silica gel using a DCM/MeOH gradient. Yield: 5.85 g (51 %).

A-15) 6-Trifluoromethyl-5-trimethylsilanylethynyl-pyridin-2-ylamine

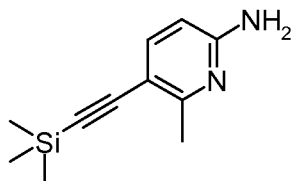
The title compound is synthesized according to general procedure GP2 starting from 5.7 g (20 mmol) 6-trifluoromethyl-5-iodo-pyridin-2-ylamine and 3.9 mL (28 mmol) 1-trimethyl-silyl-ethyne using 379 mg (2.0 mmol) CuI, 1.4 g (2.0 mmol) PdCl₂(PPh₃)₂ and 28 mL (199 mmol) triethylamine in 30 mL dry THF. For the work-up the solvent is removed under reduced pressure, the crude product is taken up in ethyl acetate and the organic phase is extracted with water. The product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 2.83 g (55 %).

A-16) 4-Methyl-5-trimethylsilanylethynyl-pyridin-2-ylamine

The title compound is synthesized according to general procedure GP2 starting from 3.3 g (14.1 mmol) 4-methyl-5-iodo-pyridin-2-ylamine and 2.8 mL (19.7 mmol)

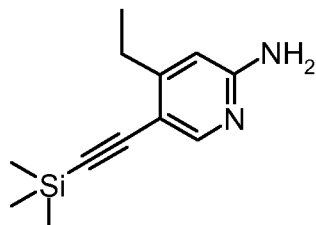
- 5 1-trimethyl-silyl-ethyne using 81 mg (1.4 mmol) CuI, 296 mg (0.42 mmol) PdCl₂(PPh₃)₂, 370 mg (1.4 mmol) triphenylphosphine and 20 mL (141 mmol) triethylamine in 25 mL dry THF. After cooling to RT, the mixture is filtered and the product is isolated from the filtrate by chromatography on silica gel using a DCM/MeOH gradient. Yield: 2.75 g (95 %).

10 **A-17) 6-Methyl-5-trimethylsilanylethynyl-pyridin-2-ylamine**



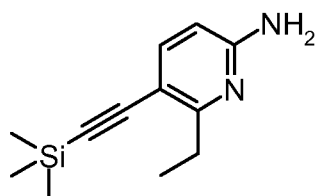
The title compound is synthesized according to general procedure GP2 starting from 5.0 g (21.4 mmol) 6-methyl-5-iodo-pyridin-2-ylamine and 4.5 mL (32 mmol)

- 15 1-trimethyl-silyl-ethyne using 407 mg (2.1 mmol) CuI, 2.0 g (2.1 mmol) Pd(PPh₃)₄ and 30 mL (214 mmol) triethylamine in 40 mL dry DMF. For the work-up the solvent is removed under reduced pressure and the product is purified twice by chromatography on silica gel using a DCM/MeOH gradient. Yield: 4.2 g (96 %).

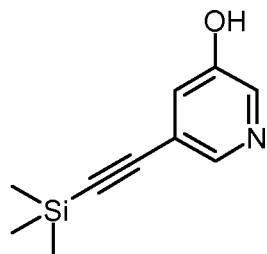
A-18) 4-Ethyl-5-trimethylsilanylethynyl-pyridin-2-ylamine

The title compound is synthesized according to general procedure GP2 starting from 10.3 g (41.6 mmol) 4-ethyl-5-iodo-pyridin-2-ylamine and 8.2 mL (58.2 mmol)

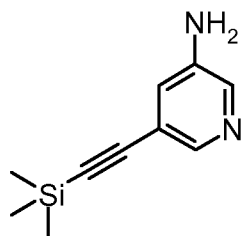
- 5 1-trimethyl-silyl-ethyne using 792 mg (4.2 mmol) CuI, 2.9 g (4.2 mmol) PdCl₂(PPh₃)₂ and 58 mL (416 mmol) triethylamine in 140 mL dry THF. For the work-up the solvent is removed under reduced pressure, the crude product is taken up in ethyl acetate and the organic phase is extracted with water. The product is purified twice by chromatography on silica gel using a cyclohexane/ethyl acetate gradient. Yield: 9.08 g (100 %).

10 A-19) 6-Ethyl-5-trimethylsilanylethynyl-pyridin-2-ylamine

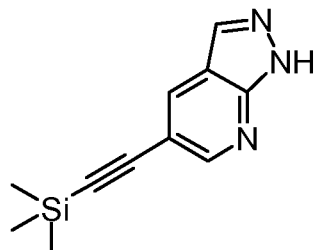
The title compound is synthesized according to general procedure GP2 starting from 18 g (72.6 mmol) 6-ethyl-5-iodo-pyridin-2-ylamine and 14.4 mL (102 mmol) 1-trimethyl-silyl-ethyne using 1.38 g (7.3 mmol) CuI, 5.1 g (7.3 mmol) PdCl₂(PPh₃)₂ and 101 mL
15 (726 mmol) triethylamine in 100 mL dry THF. For the work-up the solvent is removed under reduced pressure, the crude product is taken up in ethyl acetate and the organic phase is extracted with water. The product is purified twice by chromatography on silica gel using a cyclohexane/ethyl acetate gradient. Yield: 12.73 g (80 %).

A-20) 5-Trimethylsilanylethynyl-pyridin-3-ol

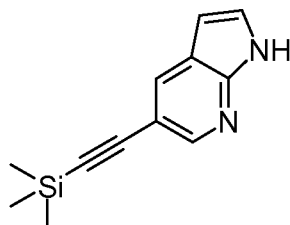
The title compound is synthesized according to general procedure GP2 starting from 2.0 g (11.6 mmol) 5-bromo-3-hydroxy-pyridine and 2.3 mL (16.2 mmol) 1-trimethylsilyl-ethyne using 66 mg (0.3 mmol) CuI, 303 mg (1.2 mmol) triphenylphosphine, 243 mg (0.3 mmol) PdCl₂(PPh₃)₂ and 19 mL (139 mmol) triethylamine in 20 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate and small amounts of cyclohexane, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 2.0 g (91 %).

A-21) 5-Trimethylsilanylethynyl-pyridin-3-ylamine

The title compound is synthesized according to general procedure GP2 starting from 2.0 g (11.6 mmol) 5-bromo- pyridin-3-ylamine and 2.3 mL (16.2 mmol) 1-trimethylsilyl-ethyne using 66 mg (0.3 mmol) CuI, 303 mg (1.2 mmol) triphenylphosphine, 243 mg (0.3 mmol) PdCl₂(PPh₃)₂ and 19 mL (139 mmol) triethylamine in 20 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate and small amounts of cyclohexane, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using a DCM/MeOH gradient. The product precipitated on the column and was subsequently extracted from the silica gel with pure MeOH. Yield: 2.0 g (91 %).

A-22) 5-Trimethylsilanylethynyl-1H-pyrazolo[3,4-*b*]pyridine

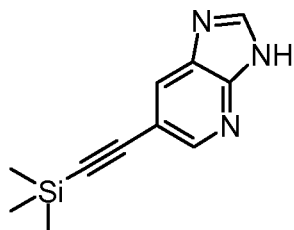
The title compound is synthesized according to general procedure GP2 starting from 1.0 g (5.1 mmol) 5-bromo-1H-pyrazolo[4,5-*b*]pyridine and 1.0 mL (7.1 mmol) 1-trimethylsilyl-ethyne using 29 mg (0.15 mmol) CuI, 133 mg (0.51 mmol) triphenylphosphine, 106 mg (0.15 mmol) PdCl₂(PPh₃)₂ and 8.4 mL (60.6 mmol) triethylamine in 8 mL dry THF. The formed precipitate is filtered off and the product is purified by RP-HPLC using an ACN/H₂O gradient. Yield: 542 mg (50 %).

A-23) 5-Trimethylsilanylethynyl-1H-pyrrolo[2,3-*b*]pyridine

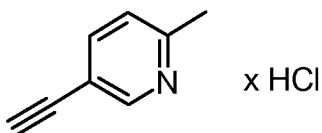
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The title compound is synthesized according to general procedure GP2 starting from 3.0 g (15.2 mmol) 5-bromo-1H-pyrrolo[2,3-*B*]pyridine and 3.0 mL (21.3 mmol) 1-trimethyl-silyl-ethyne using 87 mg (0.46 mmol) CuI, 400 mg (1.5 mmol) triphenylphosphine, 312 mg (0.46 mmol) PdCl₂(PPh₃)₂ and 25.4 mL (182 mmol) triethylamine in 25 mL dry THF. The formed precipitate is filtered off and the product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 3.05 g (94 %).

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A-24) 6-Trimethylsilanylethynyl-3H-imidazo[4,5-b]pyridine

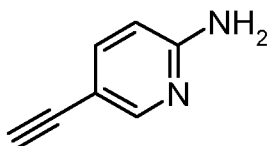
The title compound is synthesized according to general procedure GP2 starting from 1.2 g (6.1 mmol) 5-bromo-3H-imidazo[4,5-b]pyridine and 1.2 mL (8.4 mmol) 1-trimethylsilyl-ethyne using 34 mg (0.18 mmol) CuI, 159 mg (0.61 mmol) triphenylphosphine, 128 mg (0.18 mmol) PdCl₂(PPh₃)₂ and 10.1 mL (72.7 mmol) triethylamine in 10 mL dry THF. The formed precipitate is filtered off and the product is purified by RP-HPLC using an ACN/H₂O gradient. Yield: 606 mg (46 %).

A-25) 5-Ethynyl-2-methyl-pyridine

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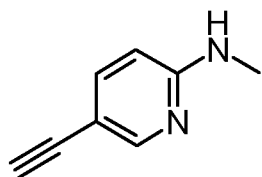
The title compound is synthesized according to general procedure GP3 starting from 2.2 g (12 mmol) 2-methyl-5-trimethylsilanylethynyl-pyridine and 0.80 g (5.8 mmol) K₂CO₃ in 13 mL MeOH. The crude product is purified by chromatography on silica gel using a cyclohexane/ethyl acetate gradient. The product is extracted from the organic phase with 1 N HCl and isolated as the hydrochloride after lyophilization. Yield: 1.3 g (73 %).

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A-26) 5-Ethynyl-pyridin-2-ylamine

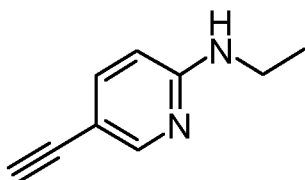
The title compound is synthesized according to general procedure GP3 starting from 5.5 g (29 mmol) 5-trimethylsilanylethynyl-pyridin-2-ylamine and 2.0 g (14 mmol) K_2CO_3 in 30 mL MeOH. The product is purified by chromatography on silica gel using a hexane/ethyl acetate gradient. Yield: 2.9 g (85 %).

5 **A-27) (5-Ethynyl-pyridin-2-yl)-methyl-amine**



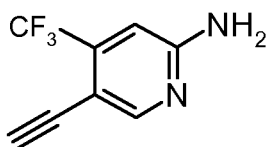
The title compound is synthesized according to general procedure GP3 starting from 1.5 g (7.3 mmol) methyl-(5-trimethylsilanylethynyl-pyridin-2-yl)-amine and 507 mg (3.7 mmol) K_2CO_3 in 10 mL MeOH. Yield: 698 mg (56 %) after chromatography on silica gel.

10 **A-28) (5-Ethynyl-pyridin-2-yl)-ethyl-amine**

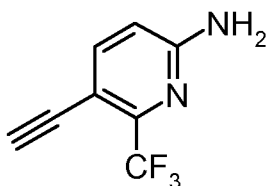


The title compound is synthesized according to general procedure GP3 starting from 980 mg (4.5 mmol) TMS-alkyne and 310 mg (2.3 mmol) K_2CO_3 in 6 mL MeOH. Yield: 388 mg (59 %) after chromatography on silica gel.

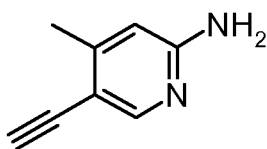
15 **A-29) 5-Ethynyl-4-trifluoromethyl-pyridin-2-ylamine**



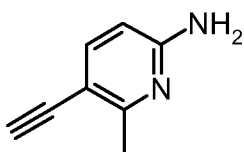
The title compound is synthesized according to general procedure GP3 starting from 5.9 g (22.6 mmol) 4-trifluoromethyl-5-trimethylsilanylethynyl-pyridin-2-ylamine and 1.56 g (11.3 mmol) K_2CO_3 in 50 mL MeOH. The product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 2.97 g (71 %).

A-30) 5-Ethynyl-6-trifluoromethyl-pyridin-2-ylamine

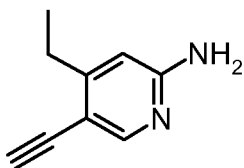
The title compound is synthesized according to general procedure GP3 starting from 2.82 g (11.0 mmol) 6-trifluoromethyl-5-trimethylsilanylethynyl-pyridin-2-ylamine and 5 757 mg (5.5 mmol) K₂CO₃ in 25 mL MeOH. The product is purified by chromatography on silica gel using a cyclohexane/ethyl acetate gradient. Yield: 0.9 g (44 %).

A-31) 5-Ethynyl-4-methyl-pyridin-2-ylamine

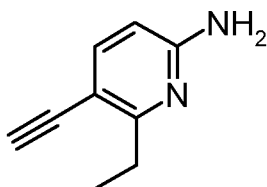
The title compound is synthesized according to general procedure GP3 starting from 10 1.8 g (8.8 mmol) 4-methyl-5-trimethylsilanylethynyl-pyridin-2-ylamine and 609 mg (4.4 mmol) K₂CO₃ in 315 mL MeOH. The product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 1.0 g (86 %).

A-32) 5-Ethynyl-6-methyl-pyridin-2-ylamine

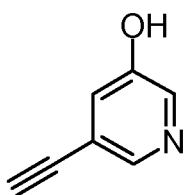
15 The title compound is synthesized according to general procedure GP3 starting from 4.3 g (21.0 mmol) 6-methyl-5-trimethylsilanylethynyl-pyridin-2-ylamine and 1.5 g (10.5 mmol) K₂CO₃ in 30 mL MeOH. The product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 3.6 g.

A-33) 4-Ethyl-5-ethynyl-pyridin-2-ylamine

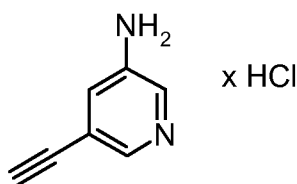
The title compound is synthesized according to general procedure GP3 starting from 3.3 g (15 mmol) 4-ethyl-5-trimethylsilanylethynyl-pyridin-2-ylamine and 1.04 g
5 (7.5 mmol) K₂CO₃ in 30 mL MeOH. The product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 1.78 g (81 %).

A-34) 6-Ethyl-5-ethynyl-pyridin-2-ylamine

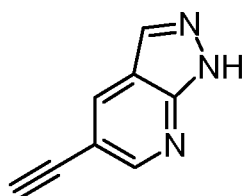
The title compound is synthesized according to general procedure GP3 starting from
10 12.23 g (56 mmol) 6-ethyl-5-trimethylsilanylethynyl-pyridin-2-ylamine and 3.87 g (28 mmol) K₂CO₃ in 120 mL MeOH. The product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 4.5 g (85 %).

A-35) 5-Ethynyl-pyridin-3-ol

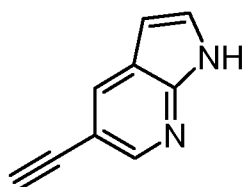
15 The title compound is synthesized according to general procedure GP3 starting from 2.0 g (10.5 mmol) TMS-alkyne and 722 mg (5.2 mmol) K₂CO₃ in 10 mL MeOH. Yield: 804 mg (49 %) after chromatography on silica gel.

A-36) 5-Ethynyl-pyridin-3-ylamine

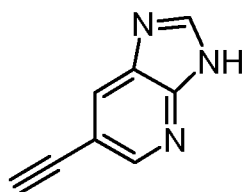
The title compound is synthesized according to general procedure GP3 starting from 2.0 g (11 mmol) TMS-alkyne and 722 mg (5.2 mmol) K₂CO₃ in 10 mL MeOH. Yield: 1.2 g (74 %) after chromatography on silica gel and precipitation from dioxane/HCl.

A-37) 5-Ethynyl-1H-pyrazolo[3,4-*b*]pyridine

The title compound is synthesized according to general procedure GP3 starting from 542 mg (2.5 mmol) TMS-alkyne and 174 mg (1.3 mmol) K₂CO₃ in 6 mL MeOH. Yield: 330 mg (92 %) after extraction.

A-38) 5-Ethynyl-1H-pyrrolo[2,3-*b*]pyridine

The title compound is synthesized according to general procedure GP3 starting from 3.1 g (14 mmol) TMS-alkyne and 983 mg (7.1 mmol) K₂CO₃ in 15 mL MeOH. Yield: 1.2 g (61 %) after chromatography on silica gel.

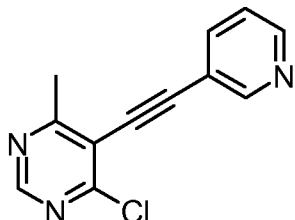
A-39) 6-Ethynyl-3H-imidazo[4,5-*b*]pyridine

The title compound is synthesized according to general procedure GP3 starting from

706 mg (3.3 mmol) TMS-alkyne and 227 mg (1.6 mmol) K_2CO_3 in 6 mL MeOH.

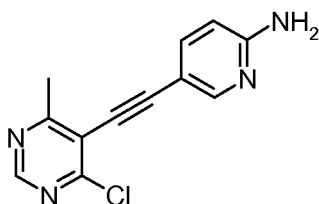
Yield: 491 mg (94 %) after extraction.

A-40) 4-Chloro-6-methyl-5-pyridin-3-ylethynyl-pyrimidine



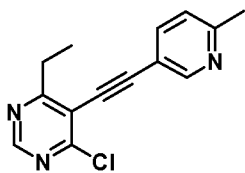
- 5 The title compound is synthesized according to general procedure GP2 starting from 250 mg (1.0 mmol) 4-chloro-5-iodo-6-methyl-pyrimidin using 123 mg (1.2 mmol) 3-ethynyl-pyridine, 18 mg (0.10 mmol) CuI, 34 mg (0.05 mmol) bis-(triphenylphosphine)palladium(II) chloride, 0.5 mL triethylamine in 2 mL DMF. The reaction mixture is stirred for 3 h at 60 °C. After removal of the solvent under reduced
10 pressure, the product is purified by PR-HPLC. Yield: 25 mg (11 %).

A-41) 5-(6-Amino-pyridin-3-ylethynyl)-4-chloro-6-methyl-pyrimidine



- The title compound can be synthesized according to general procedure GP2 starting from 30 g (0.11 mol) 4-chloro-5-iodo-6-methyl-pyrimidin (**A-1**) and 26.4 g (0.22 mol) of
15 5-ethynyl-pyridin-2-ylamine (**A-36**) using 2.1 g (11 mmol) copper iodide and 7.9 g (11 mmol) bis(triphenylphosphine)palladium chloride and triethylamine in 600 mL THF. After work up and chromatography (silica, eluent 5 % MeOH in DCM) 13 g (45 %) of the desired product is obtained.

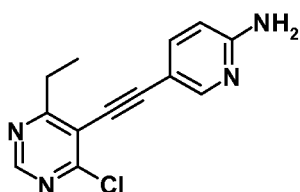
A-42) 4-Chloro-6-ethyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidine



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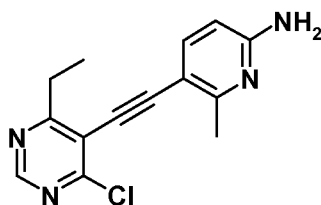
The title compound is synthesized according to general procedure GP2 starting from 250 mg (1.0 mmol) 4-chloro-6-ethyl-5-iodo-pyrimidine using 121.5 mg (1.2 mmol) 5-ethynyl-2-methyl-pyridine, 18 mg (0.10 mmol) CuI, 34 mg (0.05 mmol) bis-(triphenylphosphine)palladium(II) chloride, 0.5 mL triethylamine in 2 mL DMF. The reaction mixture is stirred for 3 h at 60 °C. After removal of the solvent under reduced pressure, the product is purified by PR-HPLC. Yield: 25 mg (11 %).

A-43) 5-(6-Amino-pyridin-3-ylethynyl)-4-chloro-6-ethyl-pyrimidine



To a stirred solution of 60 g (0.22 mol) 4-chloro-5-iodo-6-ethyl-pyrimidin (**A-2**) in 1200 mL THF under argon is added 4.2 g (22 mmol) CuI and 15.7 g (22 mmol) bis(triphenylphosphine)palladium chloride. The reaction mixture is purged with argon for 30 min. 15.7 g (0.22 mol) of 5-ethynyl-pyridin-2-ylamine (**A-36**) and triethylamine is added and the reaction mixture is heated at 60°C for 4 h. After work up and chromatography (silica, eluent 5 % MeOH in DCM) 26 g (45 %) of the desired product is obtained.

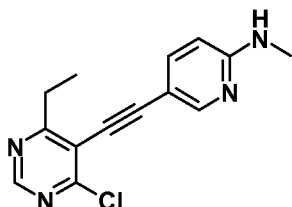
A-44) 5-(6-Amino-2-methyl-pyridin-3-ylethynyl)-4-chloro-6-ethyl-pyrimidine



The title compound is synthesized according to general procedure GP2 starting from 6.0 g (22.3 mmol) 4-chloro-6-ethyl-5-iodo-pyrimidine using 3.5 g (26.8 mmol) 5-ethynyl-6-methyl-pyridin-2-ylamine, 213 mg (1.1 mmol) CuI, 1.57 g (2.2 mmol) bis-(triphenyl-phosphine)palladium(II) chloride, 15 mL (112 mmol) triethylamine in 100 mL DME. The reaction mixture is stirred over night at RT. After removal of the solvent under reduced pressure, the residue is taken up in water and ethylacetate and the aqueous phase is extracted twice with ethylacetate. The combined organic phases are

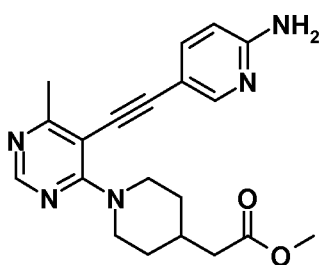
dried over MgSO_4 , filtered over silica and the solvent is removed under reduced pressure.
Yield: 2.9 g (64 %)

A-45) [5-(4-Chloro-6-ethyl-pyrimidin-5-ylethynyl)-pyridin-2-yl]-methyl-amine



- 5 The title compound is synthesized according to general procedure GP2 starting from 0.89 g (2.6 mmol) 4-chloro-6-ethyl-5-iodo-pyrimidine using 0.48 g (3.65 mmol) (5-Ethynyl-pyridin-2-yl)-methyl-amine, 40 mg (0.21 mmol) CuI , 180 mg (0.26 mmol) bis-(triphenyl-phosphine)palladium(II) chloride, 3.6 mL (26.1 mmol) triethylamine in 5.5 mL THF. The reaction mixture is stirred over night at 65°C . After removal of the
10 solvent under reduced pressure, the residue is taken up in water and ethylacetate and the aqueous phase is extracted twice with ethylacetate. The combined organic phases are dried over MgSO_4 , filtered over silica and the solvent is removed under reduced pressure. Yield: 320 mg (46 %).

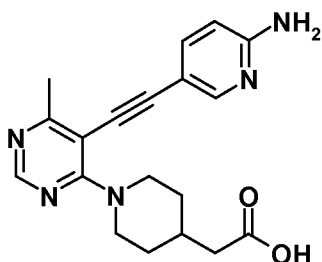
- A-88) {1-[5-(6-Amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidin-4-yl}-acetic acid methyl ester**
15



- The title compound is synthesized according to general procedure GP7 (method 2) starting from 2.0 g (8.17 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidine and 1.90 g (9.81 mmol) piperidin-4-yl-acetic acid methyl ester using 3.50 mL (20.4 mmol) DIPEA in 50 mL ACN. The reaction mixture is stirred for 1 h at 80°C .
20 The solvent is removed under reduced pressure. The residue is taken up in DCM/MeOH and filtered over silica. After removal of the solvent and extractive work up 2.9 g (96 %)

of the desired product is obtained. The product is used without further purification for the next step.

A-89) {1-[5-(6-Amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidin-4-yl}-acetic acid



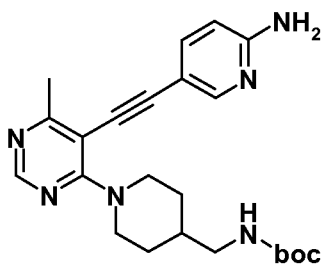
5

The title compound is synthesized according to general procedure GP8 starting from 2.87 g (7.85 mmol) {1-[5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidin-4-yl}-acetic acid methyl ester using 0.82 g (19.6 mmol) LiOH in 10 mL water and 40 mL THF. The reaction mixture is stirred over night at 50 °C. The THF is removed under reduced pressure and the residue is taken up DCM and MeOH and separated from insoluble material. The filtrate is dried over MgSO₄ and the solvent is removed under reduced pressure. After drying 2.9 g (95 %) of crude product is obtained which is used for the next step without purification.

10

A-90) {1-[5-(6-Amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidin-4-ylmethyl}-carbamic acid *tert*-butyl ester

15

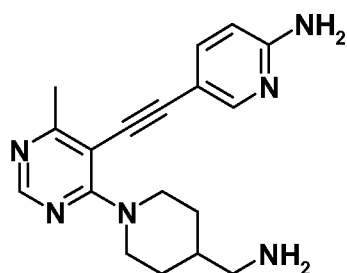


The title compound is synthesized according to general procedure GP7 (method 2) starting from 2.0 g (8.17 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidine and 2.33 g (9.81 mmol) piperidin-4-ylmethyl-carbamic acid *tert*-butyl ester using 1.82 mL (10.6 mmol) DIPEA in 50 mL ACN. The reaction mixture is stirred for 1 h at 80 °C. The solvent is removed under reduced pressure. The residue is taken up in

20

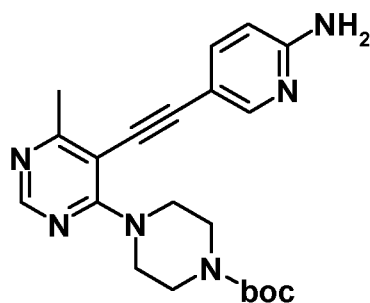
DCM/MeOH and filtered over silica. After removal of the solvent and extractive work up 3.1 g (90 %) of the desired product is obtained. The product is used without further purification for the next step.

A-91) 5-[4-(4-Aminomethyl-piperidin-1-yl)-6-methyl-pyrimidin-5-ylethynyl]-pyridin-2-ylamine



To a solution of 3.10 g (7.34 mmol) {1-[5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidin-4-ylmethyl}-carbamic acid *tert*-butyl ester in 20 mL DCM and 20 mL MeOH at RT is added 2.75 mL (11.0 mmol) 4 M HCl in dioxane. The reaction is stirred over night at 50 °C. The solvent is removed under reduced pressure and the residue is taken up in a small amount of MeOH. The precipitated product is filtered off and washed with few MeOH. After drying 3.06 g (95 %) of the desired product is obtained.

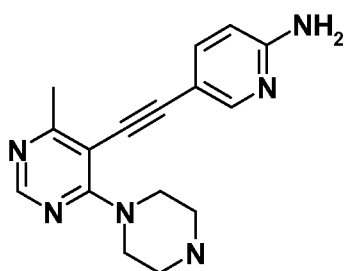
A-94) 4-[5-(6-Amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperazine-1-carboxylic acid *tert*-butyl ester



The title compound is synthesized according to general procedure GP7 (method 2) starting from 5.0 g (20.4 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidine and 4.57 g (24.5 mmol) piperazine 1-carboxylic acid *tert*-butyl ester using 10.4 mL (61.3 mmol) DIPEA in 50 mL dioxane. The reaction mixture is stirred at 80 °C

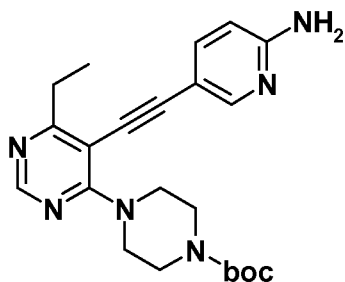
over night. The solvent is removed under reduced pressure. The residue is taken up in water extracted three times with ethylacetate. The combined organic layers are dried over MgSO₄ filtered off and the solvent is removed under reduced pressure yielding 7.5 g (94 %) of the desired product, which is used without further purification for the next step.

5 **A-95) [5-(6-Amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperazine**



A solution of 7.5 g (19.1 mmol) 4-[5-(6-Amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperazine-1-carboxylic acid *tert*-butyl ester in 50 mL 4 M HCl (in dioxane) is stirred for 3 hours at room temperature. The reaction mixture is evaporated and the residue is taken up in 50 ml DCM and washed with saturated aqueous NaHCO₃ solution. After phase separation the organic solvent is removed under reduced pressure. The residue is taken up in methanol dried over Na₂SO₄. After 15 hours the suspension is filtered off, the residue is washed with methanol and the solvent is removed under reduced pressure. After drying 5.6 g (100%) of crude product are obtained, which are used without further purification in the next step.

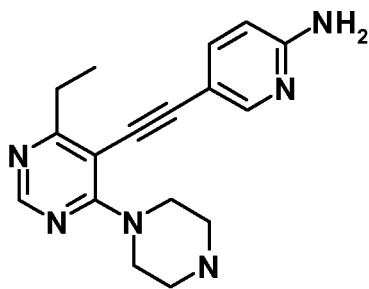
A-96) 4-[5-(6-Amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-piperazine-1-carboxylic acid *tert*-butyl ester



20

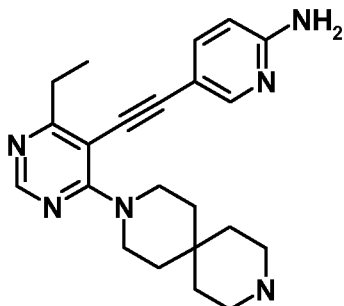
The title compound is synthesized according to general procedure GP7 (method 2) starting from 5.0 g (19.3 mmol) 4-chloro-6-ethyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidine and 4.32 g (23.2 mmol) piperazine 1-carboxylic acid *tert*-butyl ester using 9.86 mL (57.9 mmol) DIPEA in 50 mL dioxane. The reaction mixture is stirred at 80 °C
5 over night. The solvent is removed under reduced pressure. The residue is taken up in water extracted three times with ethylacetate. The combined organic layers are dried over MgSO₄ filtered off and the solvent is removed under reduced pressure. The residue is purified via NP-chromatography (DCM/MeOH 75/25 as eluent) yielding 7.2 g (92 %) of the desired product, which is used without further purification for the next step.

10 **A-97) [5-(6-Amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-piperazine**



A solution of 7.2 g (17.7 mmol) 4-[5-(6-Amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-piperazine-1-carboxylic acid *tert*-butyl ester in 50 mL 4 M HCl (in dioxane) is stirred for 3 hours at room temperature. The reaction mixture is evaporated and the
15 residue is taken up in 50 ml DCM and washed with saturated aqueous NaHCO₃ solution. After phase separation the organic solvent is removed under reduced pressure. The residue is taken up in methanol dried over Na₂SO₄. After 15 hours the suspension is filtered off, the residue is washed with methanol and the solvent is removed under reduced pressure. After drying 5.5 g (100%) of crude product are obtained, which are
20 used without further purification in the next step.

A-98) 5-[4-(3,9-Diaza-spiro[5.5]undec-3-yl)-6-ethyl-pyrimidin-5-ylethynyl]-pyridin-2-ylamine



The title compound is synthesized according to general procedure GP7 (method 2) starting from 1.0 g (3.87 mmol) 4-chloro-6-ethyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidine and 1.18 g (4.6 mmol) 3,9-diazaspiro[5.5]undecane-3-carboxylic acid *tert*-butyl ester using 1.97 mL (11.6 mmol) DIPEA in 20 mL acetonitrile. The reaction mixture is stirred at 80°C over night. 1.6 ml conc. HCl is added the reaction is stirred for 4 hours at 80°C. The solvent is removed under reduced pressure. The residue is taken up in acetonitrile and K₂CO₃ is added. The mixture is stirred at 80°C over night. The solvent is removed and the residue is taken up in DCM/water. After phase separation the organic phase is extracted twice with DCM. The combined organic layers are dried over Na₂SO₄, filtered and the solvent is removed under reduced pressure yielding 1.08 g (74 %) of crude product, which is used without further purification in the next step.

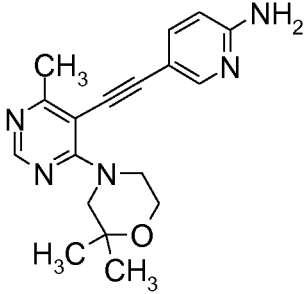
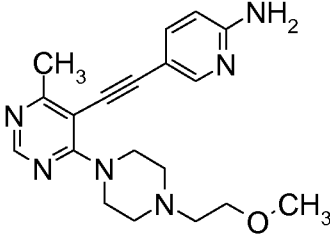
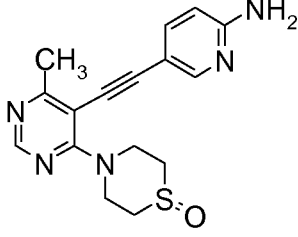
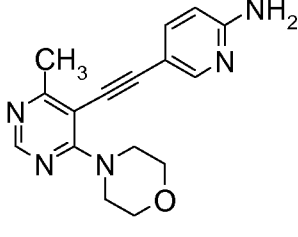
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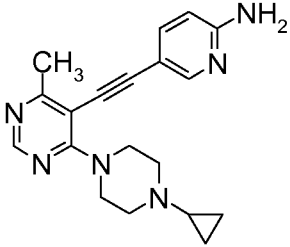
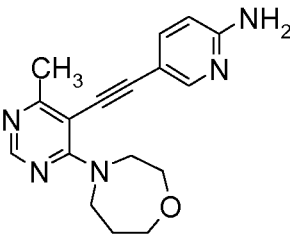
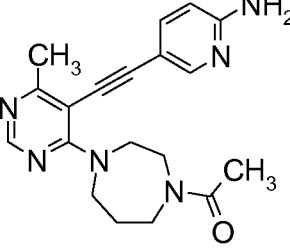
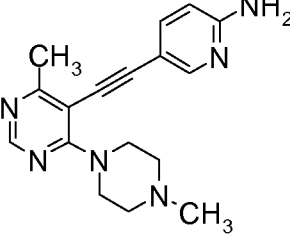
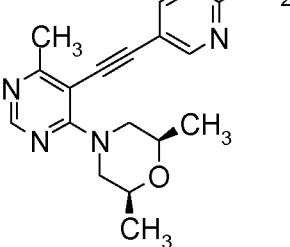
Examples B

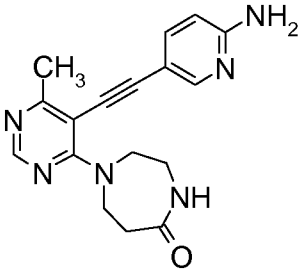
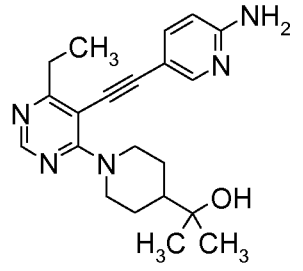
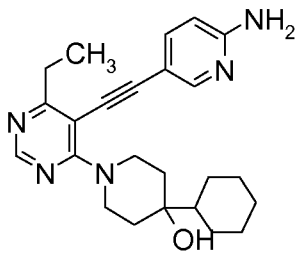
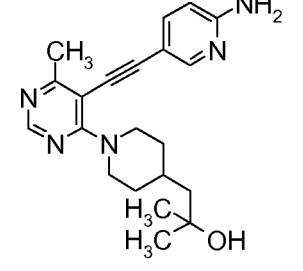
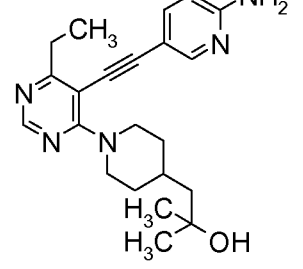
Examples B-1 to B-92 can be synthesized according to the general procedures **GP7** (nucleophilic displacement) outlined above. The appropriate halides required for synthesis can be deduced from the table of examples.

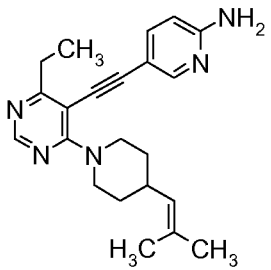
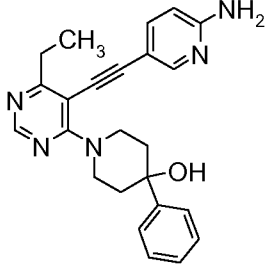
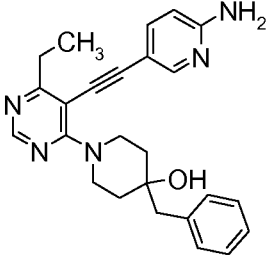
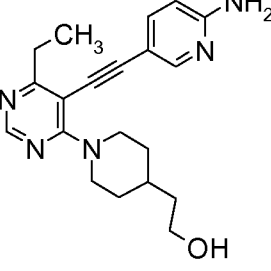
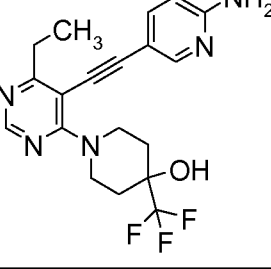
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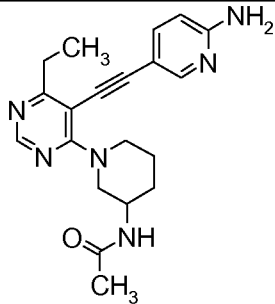
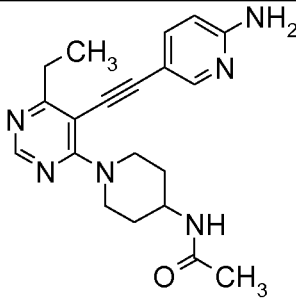
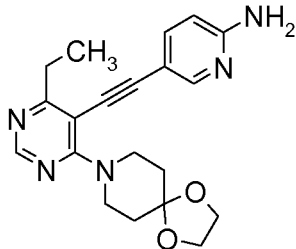
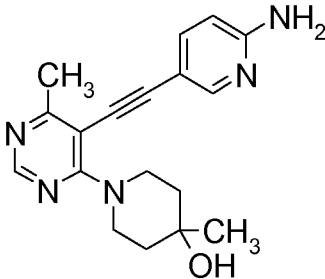
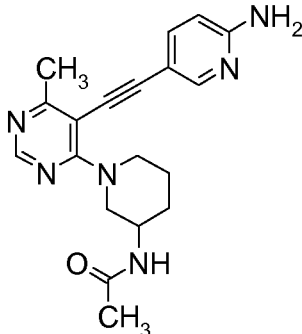
Table 1: Examples B-1 – B-87

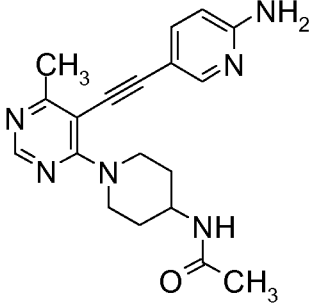
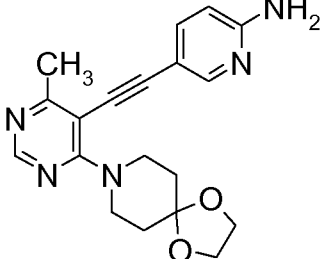
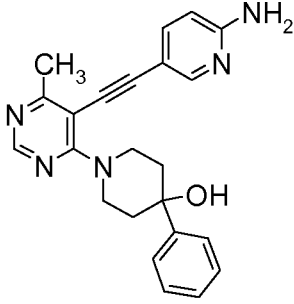
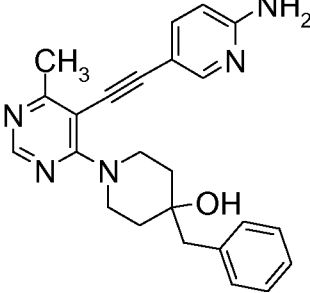
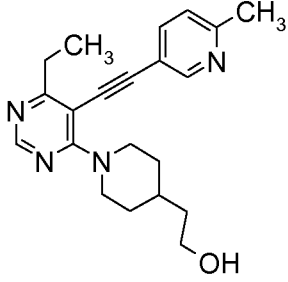
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-1		A-41	323.40	324	1,16	112
B-2		A-41	352.44	353	1,32	301
B-3		A-41	327.41	328	1,05	501
B-4		A-41	295.34	296	1,25	319

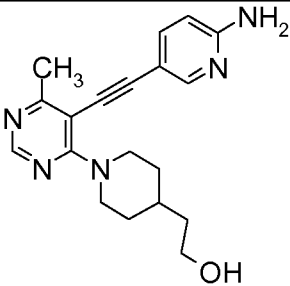
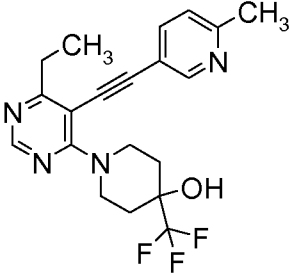
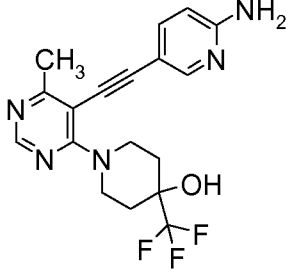
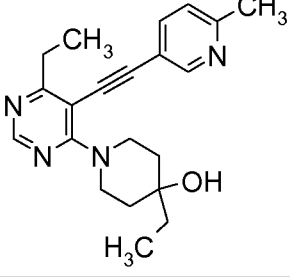
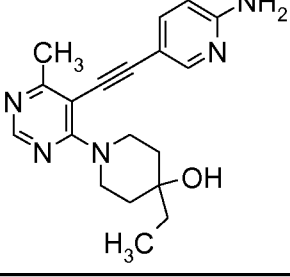
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-5		A-41	334.42	335	1,48	118
B-6		A-41	309.37	310	1,28	441
B-7		A-41	350.42	351	1,20	722
B-8		A-41	308.39	309	1,24	277
B-9		A-41	323.40	324	1,46	184

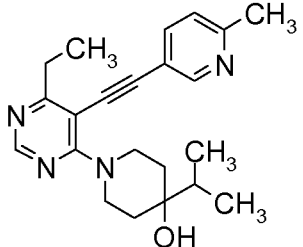
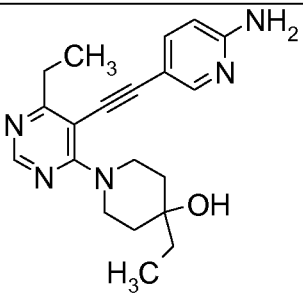
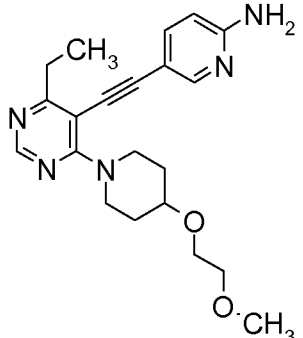
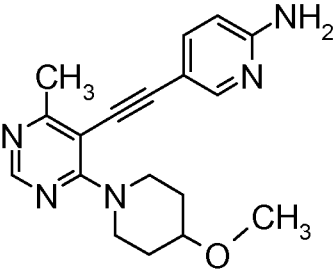
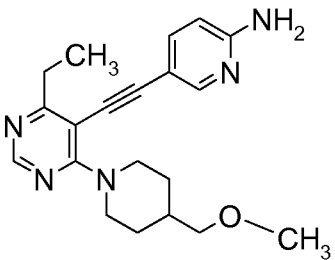
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-10		A-41	322.37	323	1,08	437
B-11		A-43	365.48	366	1,52	60
B-12		A-43	405.54	406	1,80	94
B-13		A-41	365.48	366	1,48	51
B-14		A-43	379.51	380;364	1,58; 1,52	29

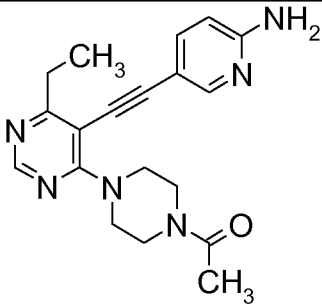
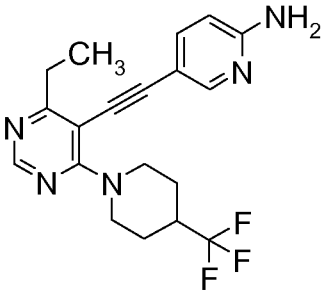
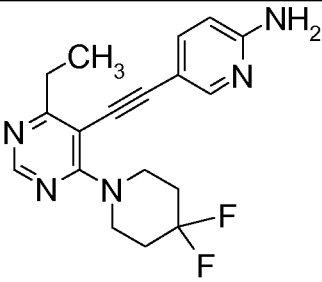
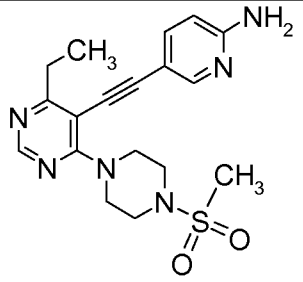
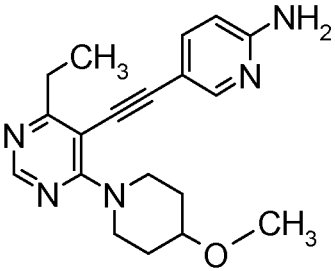
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B-15		A-43	361.49	362	2,02	202
B-16		A-43	399.50	400	1,64	34
B-17		A-43	413.52	414	1,68	129
B-18		A-43	351.45	352	1,43	34
B-19		A-43	391.40	392	1,56	3

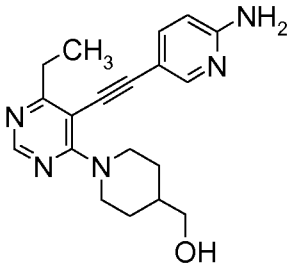
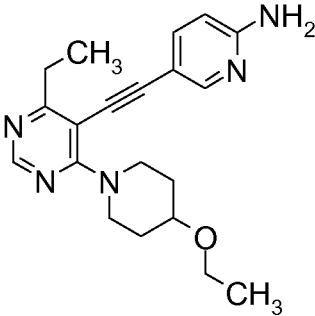
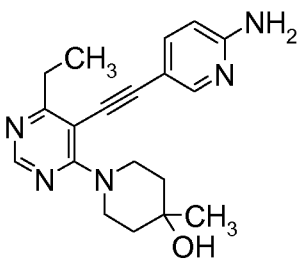
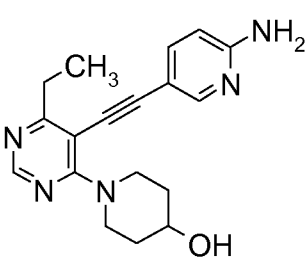
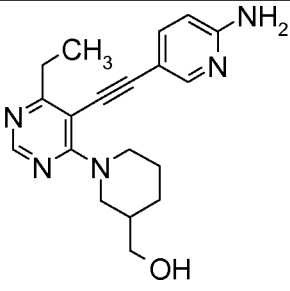
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-20		A-43	364.45	365	1,30	158
B-21		A-43	364.45	365	1,29	162
B-22		A-43	365.43	366	1,60	32
B-23		A-41	323.40	324	1,27	19
B-24		A-41	350.42	351	1,21	352

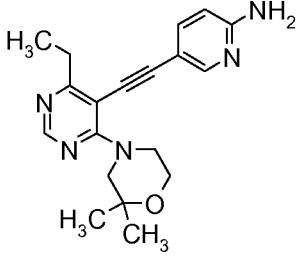
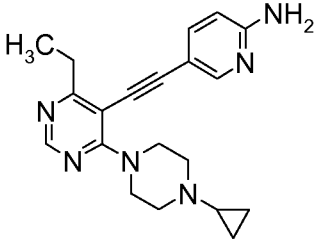
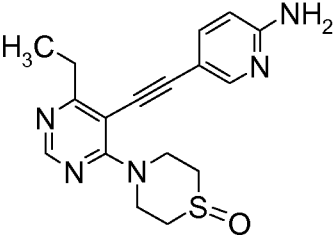
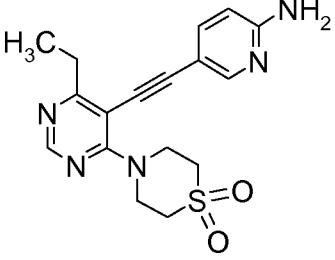
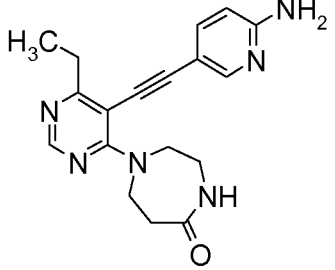
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-25		A-41	350.42	351	1,17	267
B-26		A-41	351.41	352	1,40	27
B-27		A-41	385.47	386	1,53	56
B-28		A-41	399.50	400	1,57	195
B-29		A-42	350.46	351	1,62	234

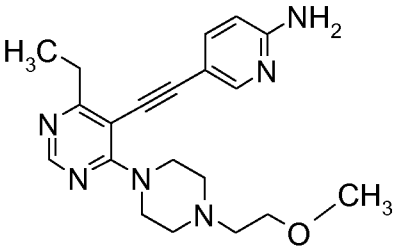
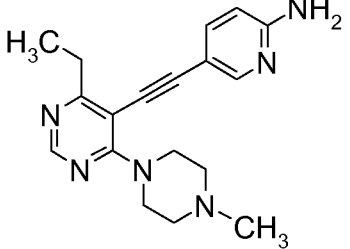
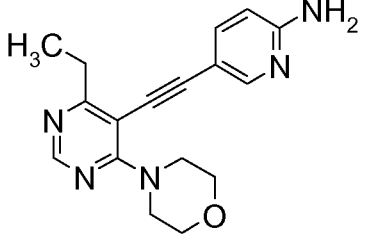
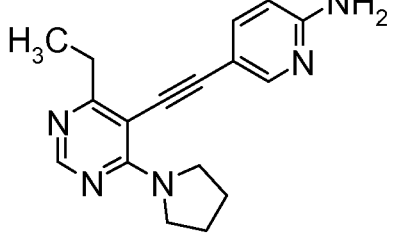
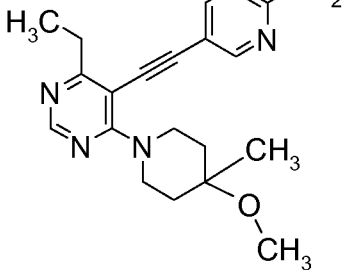
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-30		A-41	337.42	338	1,32	49
B-31		A-42	390.41	391	1,77	80
B-32		A-41	377.37	378	1,44	15
B-33		A-42	350.46	351	1,69	152
B-34		A-41	337.42	338	1,36	21

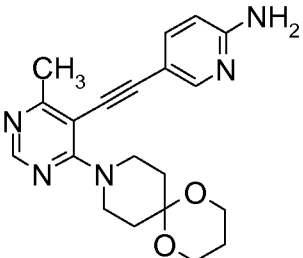
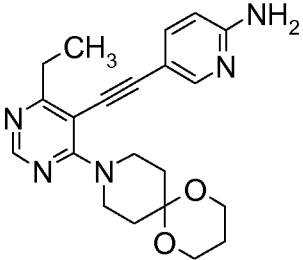
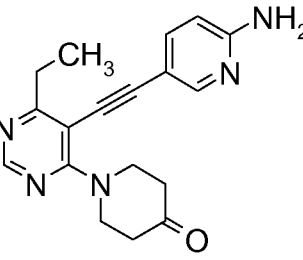
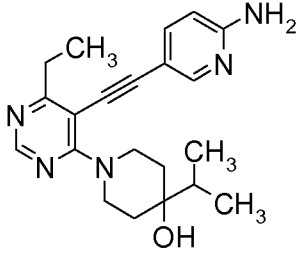
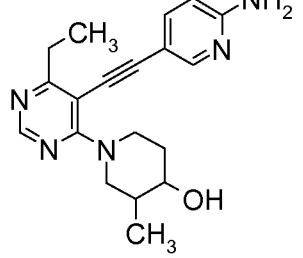
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-35		A-42	364.49	365	1,80	168
B-36		A-43	351.45	352	1,46	20
B-37		A-43	381.48	382	1,51	148
B-38		A-41	323.40	324	1,38	122
B-39		A-43	351.45	352	1,62	50

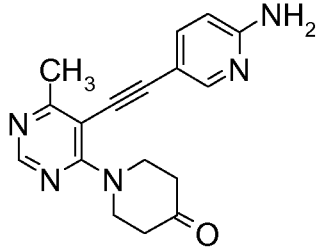
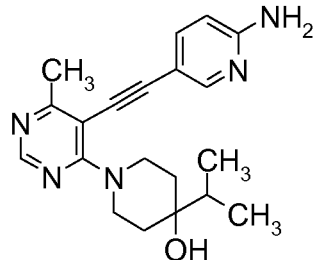
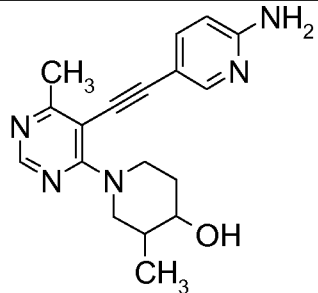
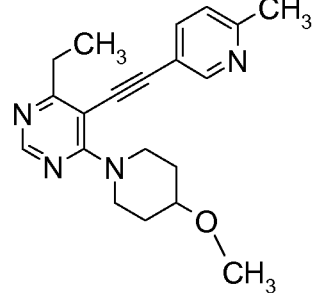
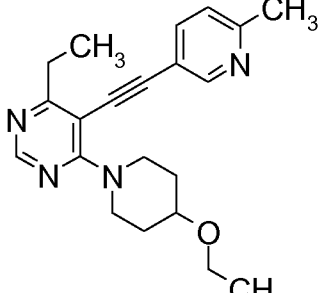
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-40		A-43	350.42	351	1,30	187
B-41		A-43	375.40	376	1,80	19
B-42		A-43	343.38	344	1,67	105
B-43		A-43	386.48	387	1,39	139
B-44		A-43	337.42	338	1,49	76

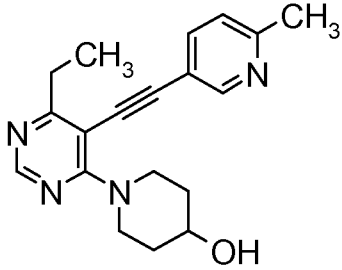
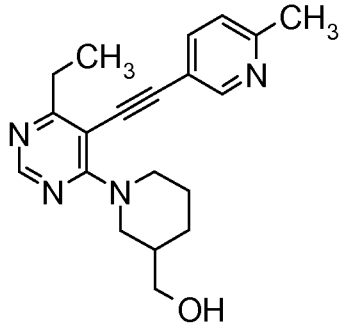
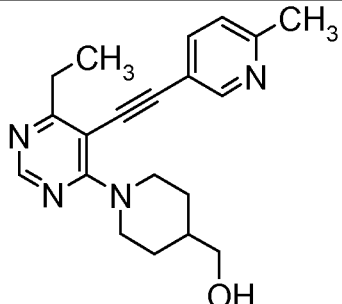
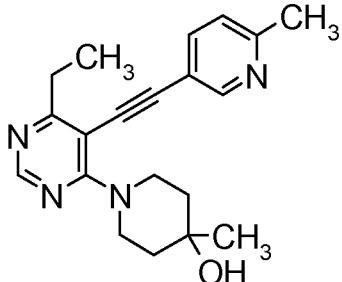
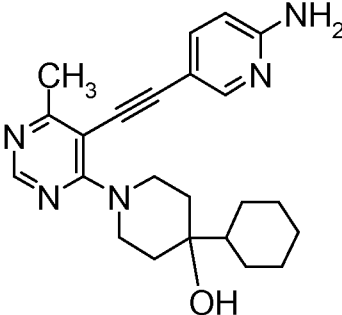
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-45		A-43	337.42	451; 338	1,26; 1,32	46
B-46		A-43	351.45	362	1,62	72
B-47		A-43	337.42	338	1,33	46
B-48		A-43	323.40	324	1,23	141
B-49		A-43	337.42	338	1,35	124

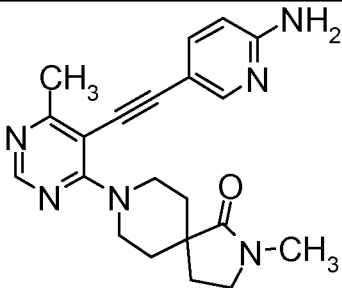
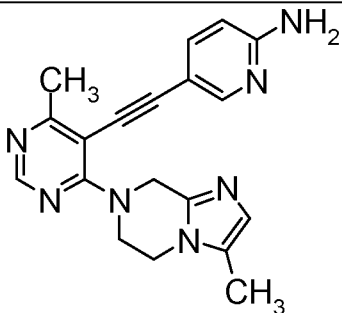
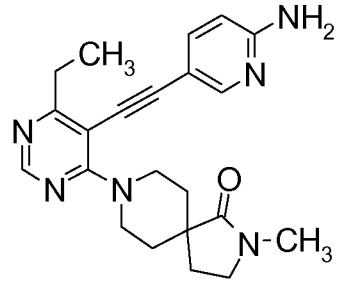
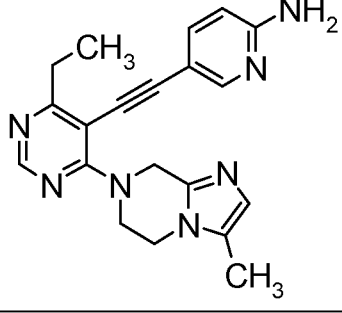
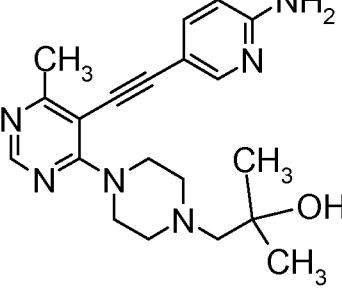
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-50		A-43	337.42	338	1,37	56
B-51		A-43	348.45	349	1.61	129
B-52		A-43	341.44	342	1.18	180
B-53		A-43	357.44	358	1,31	142
B-54		A-43	336.40	337	1.21	211

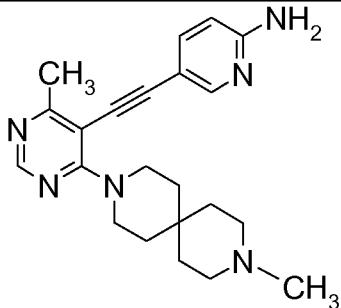
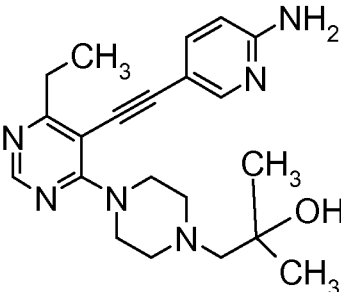
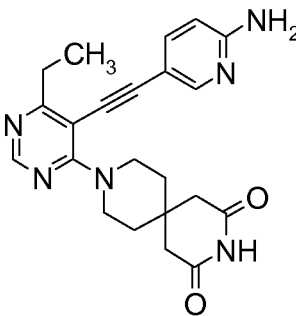
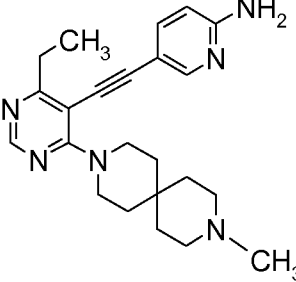
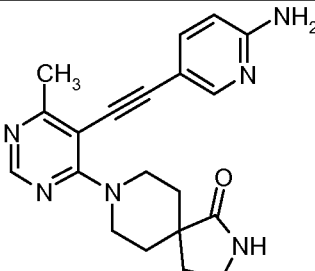
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-55		A-43	366.47	367	1.43	191
B-56		A-43	322.41	323	1.38	268
B-57		A-43	309.37	310	1.37	119
B-68A		A-43	293.37	294	1.5	492
B-69A		A-43	351.45	352	1.6	23

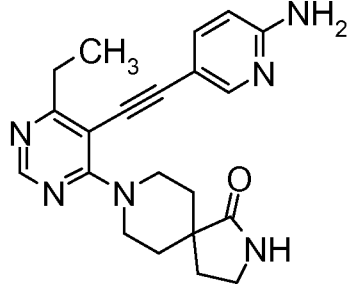
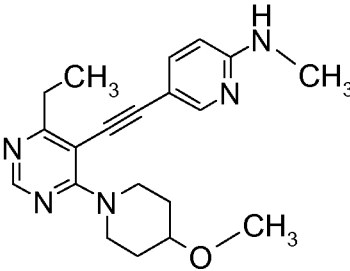
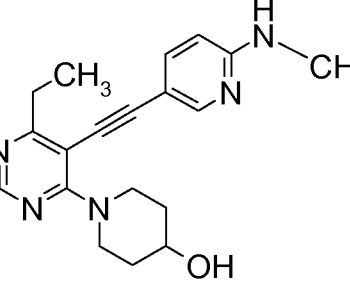
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-60		A-41	365.43	366 (245/247)	1.39 (1.31)	75
B-61		A-43	379.46	380	1,50	33
B-62		A-43	321.38	322	1.33	105
B-63		A-43	365.48	366	1.56	8
B-64		A-43	337.42	338	1.35	53

Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-65		A-41	307.36	306	1.2	218
B-66		A-41	351.45	352	1.46	24
B-67		A-41	323.40	324	1.24	174
B-68		A-42	336.44	337	1.73	589
B-69		A-42	350.46	351	1.88	783

Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-70		A-42	322.41	323	1,44	684
B-71		A-42	336.44	337	1.52	388
B-72		A-42	336.44	337	1,52	474
B-73		A-42	336.44	337	1,55	160
B-74		A-41	391.52	392	1,71	195

Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-75		A-41	376.46	377	1.32	92
B-76		A-41	345.41	346	1,27	233
B-77		A-43	390.49	391	1.41	43
B-78		A-43	359.43	360	1.39	101
B-79		A-41	366.47	367	1.42	238

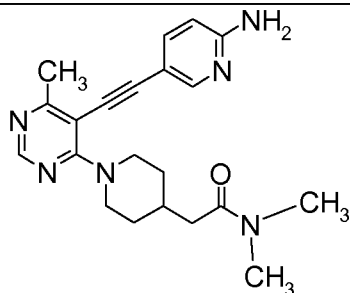
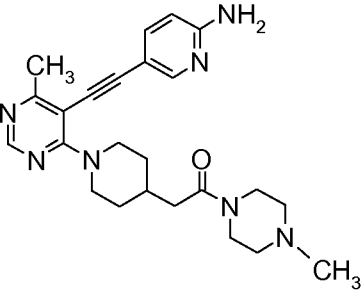
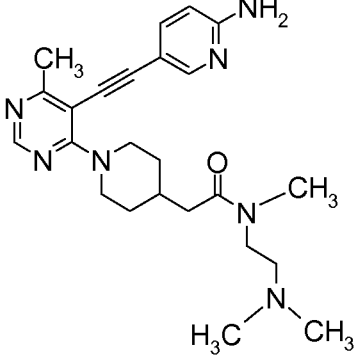
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-80		A-41	376.51	377	1.53	161
B-81		A-43	380.49	381	1.52	71
B-82		A-43	404.47	405	1.32	77
B-83		A-43	390.53	405	1.32	90
B-84		A-41	362.43	363	1,24	126

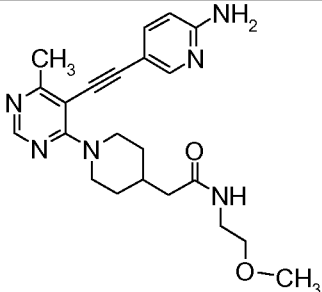
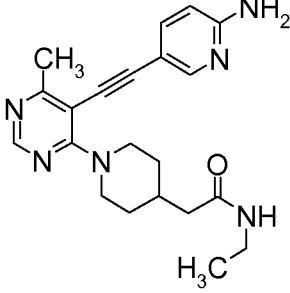
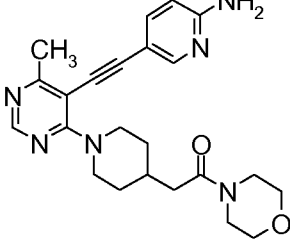
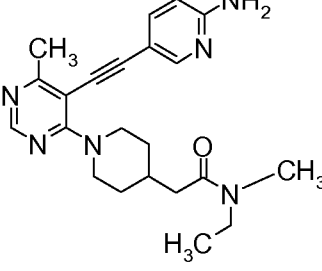
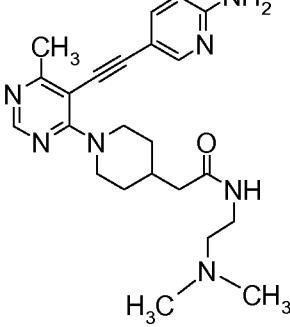
Nr.	Structure	Int.	MW	MW [M+H]	t _r [min]	EC ₅₀ PC3 [nM]
B-85		A-43	376.46	377	1,34	153
B-86		A-45	351.45	352	1,67	115
B-87		A-45	337.42	338	1,42	104

Examples E

Examples E-1 to E-8 can be synthesized according to the general procedures **GP9** (amide formation) outlined above. The appropriate intermediates required for synthesis can be deduced from the table of examples.

5 **Table 4: Examples E-1 – E-8**

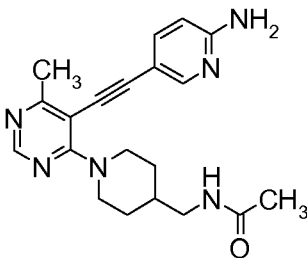
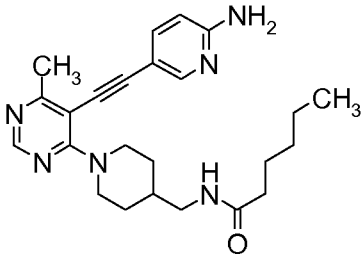
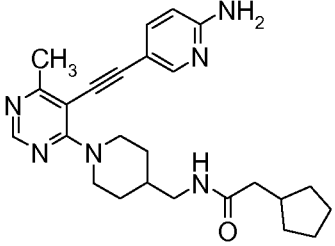
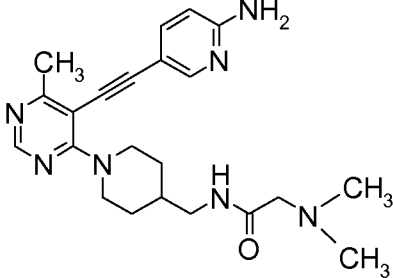
Nr.	Structure	Int.	MW [M+H]	t _R [min]	EC ₅₀ PC3 [nM]
E-1		A-89	379	1.13	221
E-2		A-89	434	1.17	nd
E-3		A-89	436	1.27	nd

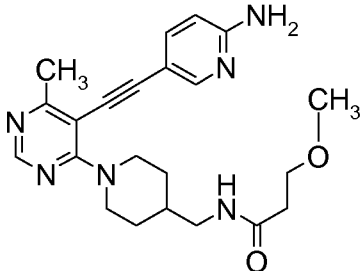
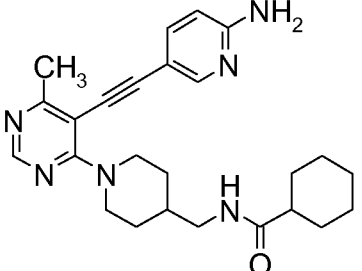
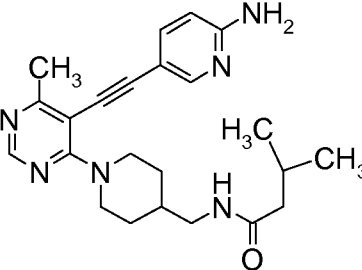
Nr.	Structure	Int.	MW [M+H]	t _R [min]	EC ₅₀ PC3 [nM]
E-4		A-89	409	1.11	300
E-5		A-89	379	1.13	171
E-6		A-89	421	1.16	358
E-7		A-89	393	1.26	266
E-8		A-89	422	1.19	nd

Examples F

Examples F-1 to F-7 can be synthesized according to the general procedures **GP10** (amide formation with acid) outlined above. The appropriate intermediates required for synthesis can be deduced from the table of examples.

5 **Table 5: Examples F-1 – F-7**

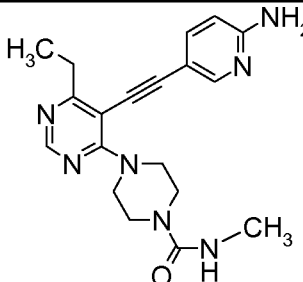
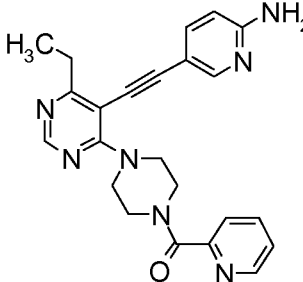
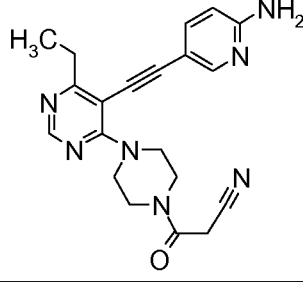
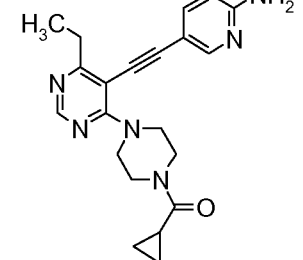
Nr.	Structure	Int.	MW [M+H]	t _R [min]	EC ₅₀ PC3 [nM]
F-1		A-91	365	1.24	135
F-2		A-91	421/ 481	1.60	344
F-3		A-91	433	1.60	335
F-4		A-91	408	1.37	nd

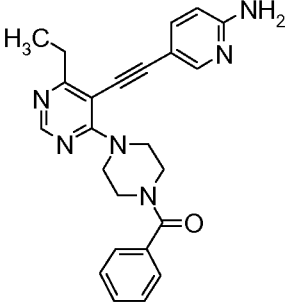
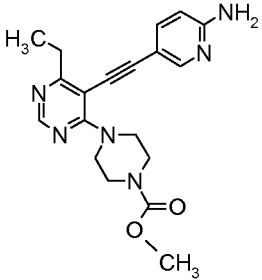
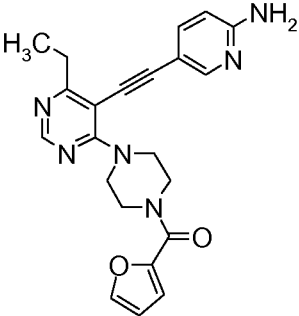
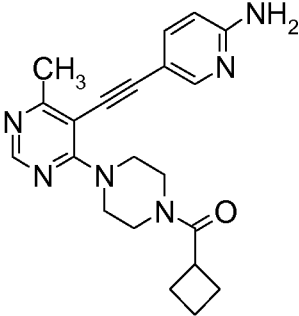
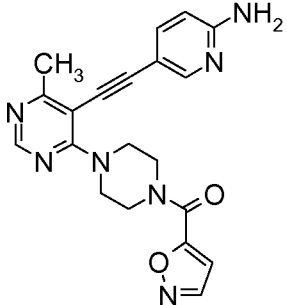
Nr.	Structure	Int.	MW [M+H]	t _R [min]	EC ₅₀ PC3 [nM]
F-5		A-91	409	1.30	141
F-6		A-91	433	1.60	277
F-7		A-91	407	1.48	nd

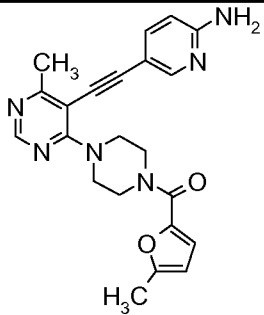
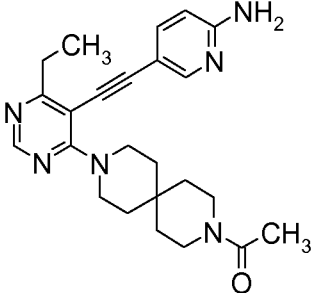
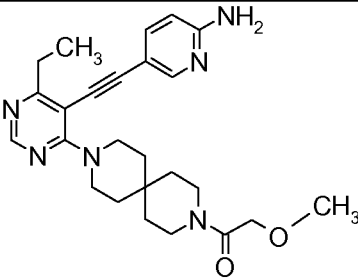
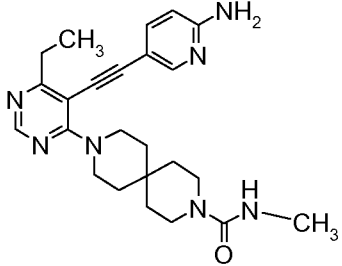
Examples G

Examples G-1 to G-13 can be synthesized according to the general procedures **GP9** (amide formation) or **GP10** (amide formation with acid) outlined above. The appropriate intermediates required for synthesis can be deduced from the table of examples.

5 **Table 6: Examples G-1 – G-13**

Nr	Structure	Int.	MW	MW [M+H]	t _R [min]	EC ₅₀ PC3 [nM]
G-1		A-97	365.44	366	1,28	212
G-2		A-97	413.48	414	1.39	138
G-3		A-97	375.43	376	1,31	550
G-4		A-97	376.46	377	1,43	206

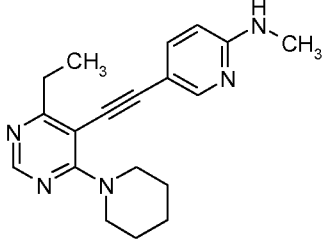
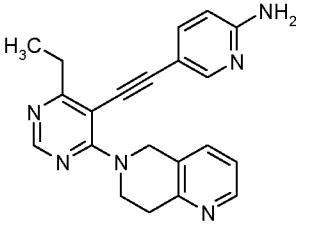
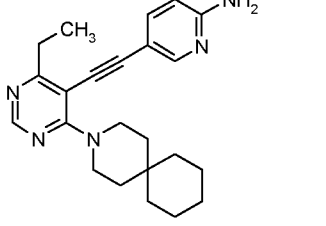
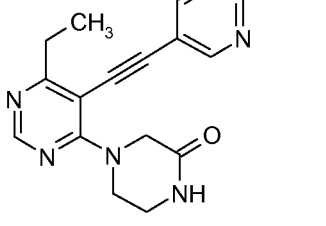
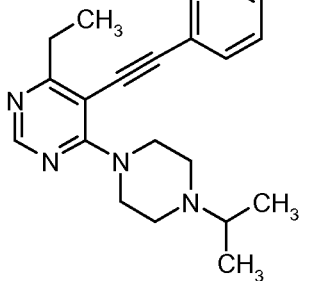
Nr	Structure	Int.	MW	MW [M+H]	t _R [min]	EC ₅₀ PC3 [nM]
G-5		A-97	412.49	413	1,58	225
G-6		A-97	366.42	367	1,47	106
G-7		A-97	402.46	403	1.48	197
G-8		A-95	376.46	377	1.29	206
G-9		A-95	389.42	390	1,16	310

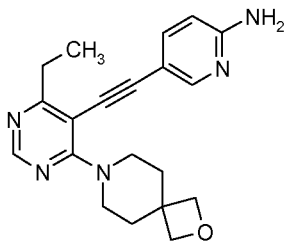
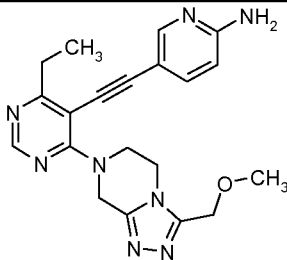
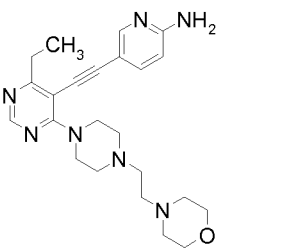
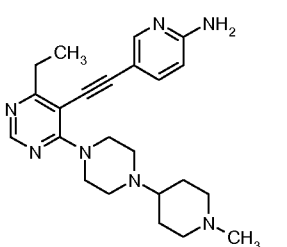
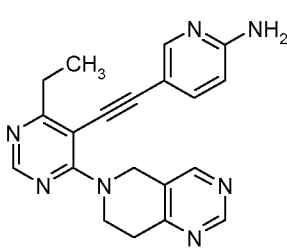
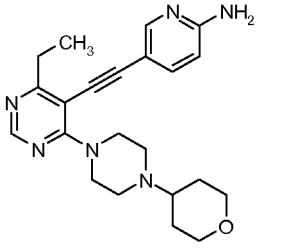
Nr	Structure	Int.	MW	MW [M+H]	t _R [min]	EC ₅₀ PC3 [nM]
G-10		A-95	402.46	403	1.31	221
G-11		A-98	418.54	419 (405)	1.50 (1.46)	55
G-12		A-98	448.57	449	1.5	41
G-13		A-98	433.56	434	1,46	53

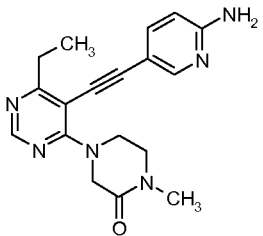
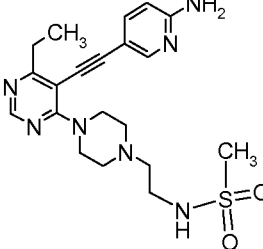
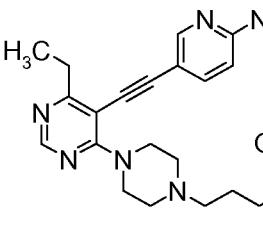
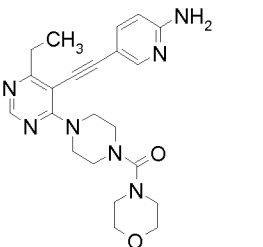
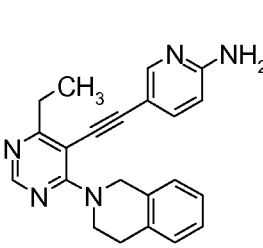
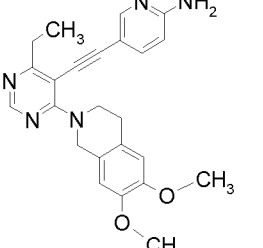
Examples H

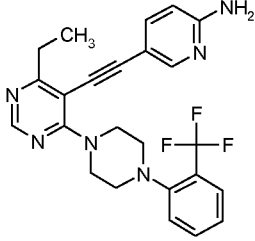
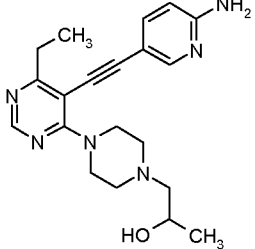
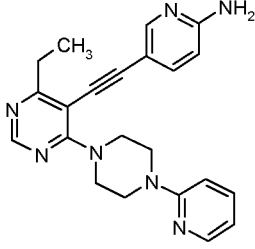
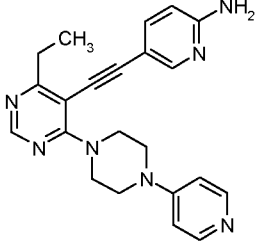
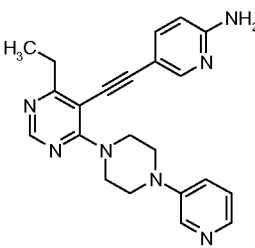
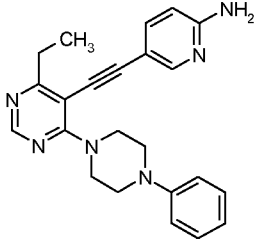
Examples H-1 to H-28 can be synthesized according to the general procedure GP7 outlined above. The appropriate intermediates for synthesis can be deduced from the table of the examples.

Table 7: Examples H-1 – H-28

Nr.	Structure	Int.	MW	MW [M+H]	t _R [min]
H-1		A-45	321.43	322	1.86
H-2		A-43	356.43	357	1.13
H-3		A-43	375.52	376	2.13
H-5		A-43	322.37	323	0.89
H-6		A-43	350.47	351	1.18

Nr.	Structure	Int.	MW	MW [M+H]	t _R [min]
H-7		A-43	349.44	350	1.07
H-8		A-43	390.45	391	0.94
H-9		A-43	421.55	422	1.03
H-10		A-43	405.55	406	1.11
H-11		A-43	357.42	358	1.01
H-12		A-43	392.5	393	1.07

Nr.	Structure	Int.	MW	MW [M+H]	t _R [min]
H-13		A-43	336.4	337	0.95
H-14		A-43	429.55	430	1
H-15		A-43	428.56	429	1.01
H-16		A-43	421.5	422	1.03
H-17		A-43	355.44	356	1.35
H-18		A-43	415.49	416	1.26

Nr.	Structure	Int.	MW	MW [M+H]	t _R [min]
H-19		A-43	452.48	453	1.53
H-20		A-43	366.47	367	1.04
H-21		A-43	385.47	386	1.23
H-22		A-43	385.47	386	1.12
H-23		A-43	385.47	386	1.14
H-24		A-43	384.48	385	1.36

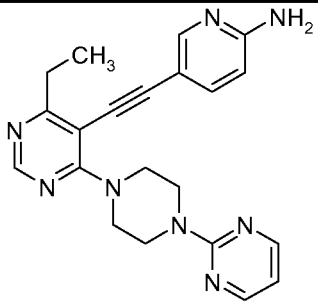
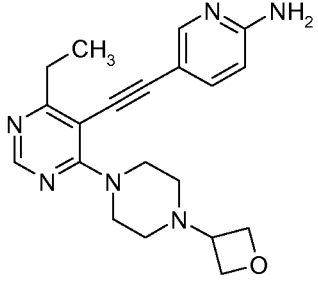
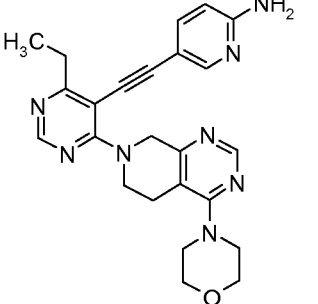
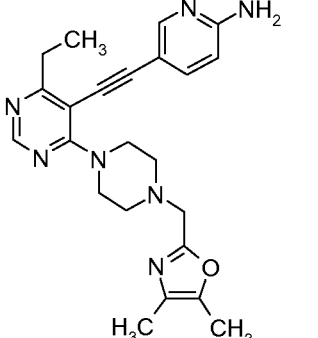
Nr.	Structure	Int.	MW	MW [M+H]	t _R [min]
H-25		A-43	386.46	387	1.19
H-26		A-43	364.45	365	1
H-27		A-43	442.52	443	1.13
H-28		A-43	417.51	418	1.18

Table 8: Biological Data of the Examples B-1 – B-87

Nr.	IC ₅₀ mTOR [nM]	IC ₅₀ PI3Ka [nM]
B-1	105	46

Nr.	IC ₅₀ mTOR [nM]	IC ₅₀ PI3Ka [nM]
B-2	32	145
B-3	83	199
B-4	38	37
B-5	10	58
B-6	72	246
B-7	94	348
B-8	56	547
B-9	11	34
B-10	41	93
B-11	7	31
B-12	16	189
B-13	18	29
B-14	9	26
B-15	64	622
B-16	7	91
B-17	74	115
B-18	5	35
B-19	1	53
B-20	16	167
B-21	19	83
B-22	4	57
B-23	7	38
B-24	46	158
B-25	42	78
B-26	10	60
B-27	23	22
B-28	50	70
B-29	67	88
B-30	9	14

Nr.	IC ₅₀ mTOR [nM]	IC ₅₀ PI3Ka [nM]
B-31	37	172
B-32	3	24
B-33	51	102
B-34	4	15
B-35	23	172
B-36	5	50
B-37	36	89
B-38	18	37
B-39	19	87
B-40	32	62
B-41	9	201
B-42	31	196
B-43	16	88
B-44	10	58
B-45	10	58
B-46	16	77
B-47	5	36
B-48	14	99
B-49	28	73
B-50	30	49
B-51	43	86
B-52	28	104
B-53	12	380
B-54	14	133
B-55	26	718
B-56	57	1551
B-57	93	46
B-58	42	131
B-59	5	53

Nr.	IC ₅₀ mTOR [nM]	IC ₅₀ PI3Ka [nM]
B-60	6	14
B-61	4	43
B-62	28	109
B-63	0,61	15
B-64	10	55
B-65	60	104
B-66	5	51
B-67	43	90
B-68	122	183
B-69	168	99
B-70	141	139
B-71	108	90
B-72	70	134
B-73	30	84
B-74	30	98
B-75	10	48
B-76	97	60
B-77	8	67
B-78	31	72
B-79	18	53
B-80	25	99
B-81	7	143
B-82	5	38
B-83	29	136
B-84	19	32
B-85	30	95
B-86	9	94
B-87	20	76

Table 9: Biological Data of the Examples E-1 – E-8

Nr.	IC₅₀ mTor [nM]	IC₅₀ PI3Ka [nM]
E-1	45	54
E-2	366	96
E-3	457	2001
E-4	144	66
E-5	58	38
E-6	59	83
E-7	53	44
E-8	261	149

5 Table 10: Biological Data of the Examples F-1 – F-7

Nr.	IC₅₀ mTOR [nM]	IC₅₀ PI3Ka [nM]
F-1	15	36
F-2	31	23
F-3	16	39
F-4	457	301
F-5	18	69
F-6	78	51
F-7	237	47

Table 11: Biological Data of the Examples G-1 – G-13

Nr.	IC₅₀ mTor [nM]	IC₅₀ PI3Ka [nM]
G-1	84	33
G-2	90	47
G-3	91	60
G-4	113	46
G-5	157	110
G-6	101	52
G-7	60	37
G-8	64	22
G-9	55	39
G-10	60	25
G-11	30	36
G-12	32	37
G-13	35	50

Table 12: Biological Data of the Examples H-1 – H-28

Nr.	IC₅₀ mTOR [nM]	IC₅₀ PI3Ka [nM]	EC₅₀ BT474 [nM]	EC₅₀ U87MG [nM]
H-1	55	214		745
H-2	67	333		
H-3	333	369		
H-4	45	58		
H-5	91	745		
H-6	15	55	72	
H-7	138	97	944	
H-8	127	185		

Nr.	IC ₅₀ mTOR [nM]	IC ₅₀ PI3Ka [nM]	EC ₅₀ BT474 [nM]	EC ₅₀ U87MG [nM]
H-9	1569	449		
H-11	27	50	93	
H-12	77	141		
H-13	37	72	76	
H-14	18	60	63	
H-15	25	108		
H-16	22	116		
H-17	68	56		
H-18	83	43		
H-19	2000	1861		
H-20	51	152	138	
H-21	33	42	68	
H-22	49	229	194	
H-23	14	48	139	
H-24	89	129	78	
H-25	14	48	15	
H-26	47	105		
H-27	139	103		
H-28	258	232		

Analytical method 1

- HPLC: Agilent 1100 Series
- 5 MS: Agilent LC/MSD SL
- column: Phenomenex, Mercury Gemini C18, 3 µm, 2.0x20 mm,
Part.No. 00M-4439-B0-CE
- solvent A: 5 mM NH₄HCO₃/ 20mM NH₃
B: acetonitrile HPLC grade

detection: MS: Positive and negative
 mass rang: 120 - 700 m/z
 fragmentor: 70
 gain EMV: 1
 5 threshold: 0.25
 UV: 315 nm
 bandwidth: 170 nm
 reference: off
 range: 210 - 400 nm
 10 range step: 2.00 nm
 peakwidth: < 0.01 min
 slit: 2 nm
 injection: 5 µL
 flow: 1.00 mL/min
 15 column temperature: 40 °C
 gradient: 0.00 min 5 % B
 0.00 – 2.50 min 5 % -> 95 % B
 2.50 – 2.80 min 95 % B
 2.81 – 3.10 min 95 % -> 5 % B

20

Analytical method 2

Instrument: Agilent 1100-SL: incl. ELSD / DAD / MSD

Chromatography:

Column: Phenomenex Gemini[®] C18, 50×2.0mm, 3µ

25 Method “Acid”

Eluent A: 0.1 % formic acid in acetonitrile

Eluent B: 0.1 % formic acid in Water

Linear Gradient program: $t_0 = 2\% \text{ A}$, $t_{3.5\text{min}} = 98\% \text{ A}$, $t_{6\text{min}} = 98\% \text{ A}$

Flow: 1 mL/min

30 Column oven temperature: 35 °C

Method "Base"

	Eluent A:	10 mM ammonia in acetonitrile
	Eluent B:	10 mM ammonia in water
	Linear Gradient program:	$t_0 = 2\% \text{ A}$, $t_{3.5\text{min}} = 98\% \text{ A}$, $t_{6\text{min}} = 98\% \text{ A}$
5	Flow:	1 mL/min
	Column oven temperature:	35 °C

Evaporative Light Scattering Detector (ELSD):

	Instrument:	Polymer Laboratories PL-ELS 2100
	Nebuliser gas flow:	1.1 L/min N ₂
10	Nebuliser temp:	50°C
	Evaporation temp:	80°C
	Lamp:	Blue LED 480 nm

Diode Array Detector (DAD):

	Instrument:	Agilent G1316A
15	Sample wavelength:	220-320 nm
	Reference wavelength:	Off

Mass Spectroscopy (MSD):

	Instrument:	Agilent LC/MSD-SL
	Ionisation:	ESI (Positive & Negative)
20	Mass range:	100-800

Abbreviations used

ACN	acetonitrile	min	minute(s)
bu	butyl	mL	millilitre
CDI	carbonyl diimidazole	MS	mass spectrometry
d	day(s)	N	normal
DC	thin layer chromatography	NIS	<i>N</i> -iodosuccinimide
DCM	dichloromethane	NMP	<i>N</i> -methylpyrrolidinone
DIPEA	diisopropylethyl amine	NMR	nuclear resonance spectroscopy
DME	dimethylether	NP	normal phase

DMF	<i>N,N</i> -dimethylformamide	ppm	part per million
DMSO	dimethylsulphoxide	R _f	retention factor
eq.	equivalent	RP	reversed phase
EtOH	ethanol	prep	preparative
h	hour(s)	RT	room temperature
HPLC	high performance liquid chromatography	<i>tert</i>	tertiary
LC	liquid chromatography	t _R	retention time
M	molar	THF	tetrahydrofuran
MeOH	methanol	TMS	Tetramethylsilanyl
Int.	Intermediate	PI3Ka	PI3K α or PI3K α

The Examples that follow describe the biological activity of the compounds according to the invention without restricting the invention to these Examples. All the EC₅₀ and IC₅₀ values listed herein are indicated in nM (nanomoles).

mTOR Kinase Activity Assay

(Phosphorylation status of mTOR substrate 4E-BP1; TR-FRET)

mTOR assay described herein provides IC₅₀ values indicating the activity of the compounds inhibiting mTOR activity. Inhibition of mTOR is expected to be indicative of acitivity in treating conditions of excessive or anomalous cell proliferation such as cancer.

Assay Principle:

The mTOR kinase TR-FRET assay utilizes a physiologically relevant protein substrate for mTOR (4E-BP1, labeled with an acceptor fluorophore (Green Fluorescent Protein) and paired with a corresponding Tb-labeled phospho-specific antibody.

The assay itself is divided into two phases: the reaction phase and the detection phase. In the reaction phase, all components required for the kinase reaction are added to the well,

including the labeled protein substrate. The reaction is allowed to incubate for 60 minutes. After the reaction, EDTA is added to stop the kinase reaction, and terbium-labeled antibody is added to bind phosphorylated product. Because the terbium chelate is stable at the EDTA concentrations used to stop a kinase assay, the antibody and EDTA can be pre-mixed prior to addition to minimize pipetting steps. Binding of the terbium labeled antibody to the fluorophore-labeled phosphorylated product brings the terbium and GFP into proximity, resulting in an increase in TR-FRET. In the presence of an inhibitor, formation of phosphorylated product is reduced, and the TR-FRET value is decreased.

10

Materials:

-GFP-4E-BP1 substrate; Invitrogen order no. PV4759

-Lanthascreen Tb-anti-p4E-BP1 (pThr46) Antibody Kit; Invitrogen order no. PV4758

-FRAP1 (mTOR) kinase; Invitrogen order no. PV4753

15 -ATP 10mM

-5x Assay Buffer (250mM HEPES pH7.5, 0.05% Polysorbate 20, 5mM EGTA, 50mM MnCl₂)

-EDTA 500mM

20 **Determining IC₅₀ Values for Test Compounds:****Kinase reaction conditions**

400 nM GFP-4E-BP1, 8 μM ATP, ~150 ng/mL mTOR, 50 mM HEPES

pH 7.5, 0.01% Polysorbate 20, 1 mM EGTA, 10 mM MnCl₂, and variable amounts of

25 test compounds.

Preparation of Reagents

Note: Thaw and keep mTOR, the substrate, ATP, and the antibody on ice prior to making working dilutions. Working dilutions of these components can be kept at room

30 temperature for short periods of time the day of use.

1. Add 2 ml of 5X Assay Buffer to 8 ml water to prepare 10 ml of **1X Assay Buffer**, wherein the concentration of **1X Assay Buffer** is 50 mM HEPES pH 7.5, 0.01% Polysorbate 20, 1 mM EGTA, and 10 mM MnCl₂.
2. Prepare **Antibody/EDTA Solution** by first adding 2.75 µl of Tb-anti p4E-BP1
5 Antibody to 2397 µl of LanthaScreen™ TR-FRET Dilution Buffer. Then, add 100 µl of 0.5 M EDTA.
3. Prepare **4X Substrate/Enzyme Solution** by first adding 72 µl of GFP-4E-BP1 (22 µM) to 926 µl of 1X Assay Buffer. Then, add 1.6 µl of mTOR (0.45 mg/mL).
4. Prepare **ATP Solution** by adding 3.2 µl of 10 mM ATP to 1997 µl of 1X Assay Buffer.

10

Serial Dilution of Inhibitors (16 point curve)

Inhibitors are serially diluted in DMSO, then diluted to a 4X working concentration with 1X Assay Buffer.

1. Dispense 40 µl of DMSO to two adjacent columns of a 96 well plate per compound
15 (e.g. columns 1 and 2).
2. Add 10 µl of inhibitor stock (10 mM) to the first well of the first column (A1) and mix.
3. Remove 10 µl from A1 and transfer to the adjacent well in the next column (B1) and mix.
4. Remove 10 µl from B1 and transfer to the next well in the first column (B2) and mix.
- 20 5. Repeat this dilution pattern through well H1 and leave the last well (H2) as DMSO only.
6. Remove 4 µl of diluted compounds and add to 96 µl of 1X Assay Buffer in a 96-well plate making 4X compound dilutions.

Kinase Reaction

1. Add 2.5 µl of 4X compound dilutions to a 384-well plate.
2. Add 2.5 µl of 4X Enzyme/Substrate Solution.
4. Preincubate for 30 min. at RT (shaker).
5. Add 5 µl of ATP Solution to all wells to start reactions.
- 30 6. Shake the assay plate on a plate shaker for 30 seconds.
7. Incubate the assay plate for one hour at room temperature (20–25°C).

Stop Step and Fluorescence Detection

1. Add 10 µl of Antibody/EDTA Solution to each well in columns 1-9.
2. Shake the assay plate on a plate shaker for 30 seconds.
- 5 3. Incubate the assay plate for one hour at room temperature (20–25°C).
4. Measure the GFP (FRET) and terbium (reference) emission signals on a fluorescence plate reader (e.g. Perkin Elmer Envision).

Data Analysis

- 10 1. Calculate the emission ratio for each sample by dividing the GFP (FRET) signal by the terbium (reference) signal.
2. Plot the concentration of each compound versus the emission ratio. Determine the concentration of compound required to reach 50% of the maximum signal (IC₅₀).
Determination of IC₅₀ values can be obtained by curve fitting (sigmoidal dose response,
15 variable slope) using Prism software from GraphPad).

Inhibition of PI3Kalpha-induced PIP-2 phosphorylation

- PI3Kalpha assay described herein provides IC₅₀ values indicating the activity of the compounds inhibiting PI3 kinase alpha activity. Inhibition of PI3 kinase is expected to be
20 indicative of activity in treating conditions of excessive or anomalous cell proliferation, such as cancers. See also J. A. Engelman, Nature Reviews Cancer, 2009, **9**, 550-562; A. Carnero, Expert Opin. Investig. Drugs, 2009, **18**, 1265-1277 and P. Liu et al., Nature Reviews Drug Discovery, 2009, **8**, 627-64.

- 25 Method type: Filter-Binding-Assay

1. Materials

- Assay buffer: 40 mM HEPES pH 7.5 SIGMA H-3375
100 mM NaCl Merck 1.064.041.000
30 1 mM EGTA SIGMA E-4378

1 mM β -Glycerophosphate SIGMA G-6253

7 mM MgCl₂ Merck 58.331.000

1 mM DTT SIGMA D-0632

(0.1% BSA only during preparation of Lipidmix after ultrasonication)

5 Phospholipid blend mix (= substrate) from Avanti Polar Lipids (#790770):

Phosphatidylinositol-4,5-bisphosphate (# 840046) 3,665%

Phosphatidylethanolamine (# 83022) 39,26%

Phosphatidylserine (# 830032) 36,66%

Sphingomyeline (# 860062) 3,665%

10 Phosphatidylcholine (# 830053) 16,75%

Per aliquot lipid (16,6mg): 26ml assay buffer + 520 μ l BSA (5%)

PI3 Kinase alpha is expressed in SF9 insect cells, coinfecting with viruses encoding p85alpha and His-p110alpha, purified by combined Ni-affinity and anion exchange chromatography). Aliquoted in desired amounts and stored at -80°C. Final assay

15 concentration 25ng/well.

Phosphotyrosin PDGFRbeta-peptide H-CGG-pY-MDMSKDESVD-pY-VPMLDM-NH₂ was synthesized by Jerini Peptide Technologies (JPT) and used in a final conc. of 1,7 μ M (stock 100 μ M prepared in Assay buffer with DTT, aliquoted in desired amounts and stored at -80°C)

20 Cold ATP (from Sigma; A-7699), 100 μ M stocksolution in H₂O, use 1 μ M final concentration in assay

[33P]-ATP, 370 MBq/ml from Amersham (#AH9968), use 0.5 μ Ci/well (10mCi/ml)

Clear 96-well plates from Greiner (# 655 162)

Filter plates: Perkin Elmer UniFilter GF/B # 6005177

25 Microscint 0 (from Perkin Elmer, #6013611)

2. Assay procedure

The substrate-containing lipid vesicles are dissolved to a concentration of 0.637 mg lipid blend/ml assay buffer (with BSA, freshly added) in 50ml Falcon -> keep on ice,

30 followed by ultrasonication (pulse of 15 sec followed by a pause of 10 sec, 4x).

Compounds are serially diluted in assay buffer + 6% DMSO and 10 µl of each dilution is added per well of a 96-well plate (compounds are tested in duplicates) and mixed with 30 µl of the lipid vesicles containing PDGFR-Peptide (0.5 µM final) and PI3K alpha (25 ng/well final). The mixture is then incubated for 20 minutes at room temperature.

- 5 Subsequently, 20 µl of assay buffer containing 3 µM cold ATP and 0.5 µCi/20 µl 33P-ATP are added. The plates are then incubated at room temperature for 120 minutes (shaking with 300 rpm).

The reaction mix is transferred onto filter plates using "filtermate harvester" from Packard: filter plates are rinsed with PBS, then the reaction mix is filtered onto the filter
10 plate, washed 5 times with PBS and are allowed to dry for 30-60 minutes at 50°C.

The plate bottom is sealed with Perkin Elmer white adhesive foil and 25 µl/well Microscint0 are added, the top is covered with transparent adhesive foil and the plate is measured with Wallac Trilux 1450 Microbeta Counter.

- 15 As positive control serve wells containing vehicle controls (1% DMSO in assay buffer), showing non-inhibited kinase activity (high values). Wells containing assay buffer instead of enzyme can serve as control for background activity (low values).

3. Evaluation

- 20 Calculate IC₅₀ values using the Smiley program (based on GrapPad Prism)

PC3 proliferation test

- The test is based on measurement of cellular DNA content via fluorescent dye binding. Because cellular DNA content is highly regulated, it is closely proportional to cell
25 number. The extent of proliferation is determined by comparing cell counts for samples treated with drugs with untreated controls.

- PC3 (human prostate carcinoma cell line) cells are sown in microtitre plates and incubated overnight in culture medium at 37 °C and 5 % CO₂. The test substances are diluted stepwise and added to the cells such that the total volume is 200 µL/well. Cells to
30 which diluent, but not substance, is added serve as controls. After an incubation time of 3

days, the medium is replaced by 100 μ L/well dye-binding solution and the cells are incubated at 37 °C in the dark for a further 60 min. For measuring the fluorescence, excitation takes place at a wavelength of 485 nm and the emission is measured at 530 nm. EC₅₀ values are calculated using the GraphPad Prism program.

5 AlamarBlue assay in AN3 CA cells

The alamarBlue cell assay provides EC₅₀ values indicative of the antiproliferative or cytotoxic effects of the compounds on the AN3 CA human endometrial cancer cell line.

1. Description

- 10 alamarBlue® is designed to provide a rapid and sensitive measure of cell proliferation and cytotoxicity in various human and animal cell lines. The assay is based on the reduction of alamarBlue in the reducing environment of living (metabolically active) cells. In the presence of added cytotoxic or antiproliferative compounds, the innate metabolic activity ceases.
- 15 AlamarBlue is soluble and stable in culture medium. Measurements are made fluorometrically by exciting at 530-560 nm and measuring emission at 590 nm. In reporting percent alamarBlue reduction by monitoring fluorescence, data are expressed as fluorescence emission intensity units as a function of time of incubation.

20 2. Cells and reagents

	AN3 CA cells	Human endometrial cancer cells (ATCC HTB-111)
	alamarBlue	Serotec Ltd
	PBS (w/o Ca, Mg)	Life Technologies, Gibco BRL (Cat. No. 4190-094)
	DMEM Medium	Lonza (Cat.No. BE-12-604F)
25	Fetal calf serum	Life Technologies, Gibco BRL (Cat. No. 10270-106)

3. Equipment

- 96-well plates, flat bottom (Falcon, Cat. No.: 353072)
- 30 96-well plates, U-shaped (Costar, Cat. No.: 3799)

CO₂-Incubator

Microplate Reader, Spectramax Plus, Molecular Devices

4. Typical Procedure

- 5 Day 0: Seed 3000 AN3 CA cells (DMEM/10% FCS) in 180 µl medium into a 96-well plate, flat bottom (include medium blank). Incubate plates at 37°C in a CO₂ incubator overnight.
- 10 Day 1: Dilute compounds to a concentration 100µM -> 1:5, 10 dilution steps, in 96-well plates.
Add 20 µl per well of each dilution to cells (total volume per well 200 µl; final conc. of cpds: 10µM -> 1:5; 0.5% DMSO final). If required, test further dilutions.
All concentrations are tested in duplicates.
- 15 Controls: Cells w/o cpd. (+ 20µl medium/DMSO).
Cells are incubated with compounds for 3 days.
- 20 Day 4: Add 25 µl of alamarBlue solution to each well and incubate for 5-8 hours at 37°C. Measure fluorescence by exciting at 530-560 nm and measuring emission at 590 nm.

5. Evaluation

Calculate EC₅₀ using GraphPad Prism (Fifty).

- 25 alamarBlue® assay can be used to measure the inhibition of mTOR as well as PI3Kalpha in vitro.

CyQuant assay in U87MG cells

- 30 The CyQuant assay provides EC₅₀ values indicative of the antiproliferative or cytotoxic effects of the compounds on the U87MG human glioblastoma cell line.

1. Description

The test is based on measurement of cellular DNA content via fluorescent dye binding. Because cellular DNA content is highly regulated, it is closely proportional to cell number. The extent of proliferation is determined by comparing cell counts for samples treated with drugs with untreated controls. In the assay, a DNA-binding dye in combination with a plasma membrane permeabilization reagent is used. The medium is aspirated, replaced with dye binding solution, cells are incubated for 30-60min., then fluorescence is measured (excitation at 485nm, emission detection at 530nm). Data are expressed as fluorescence emission intensity units as a function of time of incubation.

2. Cells and reagents

U-87MG cells	Human glioblastoma cells (ATCC HTB-14)
CyQuant NF assay	Invitrogen Cat.# C35006
PBS (w/o Ca, Mg)	Life Technologies, Gibco BRL (Cat. No. 4190-094)
RPMI1640 Medium	Life Technologies, Gibco BRL (Cat. No. 61870-010)
Fetal calf serum	Life Technologies, Gibco BRL (Cat. No. 10270-106)

3. Equipment

96-well plates, flat bottom (Falcon, Cat. No.: 353072)
 96-well plates, U-shaped (Costar, Cat. No.: 3799)
 CO₂-Incubator
 Microplate Reader, Wallac Victor

4. Typical Procedure

Day 0: Seed 3000 U-87MG cells (cultured in RPMI/10% FCS) in 150 µl medium into a 96-well plate, flat bottom (include medium blank). Incubate plates at 37°C in a CO₂ incubator overnight.

- Day 1: Dilute compounds to a concentration 80µM -> 1:5 in medium, 7 dilution steps, in 96-well plates.
Add 50 µl per well of each dilution (total volume per well 200 µl; final conc. of cpds: 20µM -> 1:5). If required, test further dilutions.
5 All concentrations are tested in duplicates or triplicates.
Controls: Cells w/o cpd. (+ 50µl medium+ DMSO).
Cells are incubated with compounds for 3 days.
- Day 4: Aspirate off medium and replace with 100µl of 1x dye binding solution
10 (22µl CyQuant NF dye reagent added to 11ml of 1x HBSS buffer) . Cover the microplate and incubate for 30-60min. for equilibration of dye-DNA binding. Measure the fluorescence intensity in a microplate reader (excitation at 485nm, emission detection at 530nm).

15 5. Evaluation

Calculate EC₅₀ using GraphPad Prism (Fifty)

The substances of the present invention are PI3 kinase pathway inhibitors, in particular of the serine/threonine kinase mTOR and/or members of the lipid kinase family Pi3K. On
20 account of their biological properties, the novel compounds of the general formula (1) and their isomers and their physiologically tolerated salts are suitable for treating diseases which are characterized by excessive or anomalous cell proliferation.

These diseases include, for example: viral infections (e.g. HIV and Kaposi's sarcoma); inflammation and autoimmune diseases (e.g. colitis, arthritis, Alzheimer's disease,
25 glomerulonephritis and wound healing); bacterial, fungal and/or parasitic infections; leukaemias, lymphomas and solid tumours; skin diseases (e.g. psoriasis); bone diseases; cardiovascular diseases (e.g. restenosis and hypertrophy). In addition, the compounds are useful for protecting proliferating cells (e.g. hair cells, intestinal cells, blood cells and progenitor cells) from DNA damage due to irradiation, UV treatment and/or cytostatic
30 treatment (Davis et al., 2001).

For example, the following cancer diseases can be treated with compounds according to the invention, without, however, being restricted thereto: brain tumours, such as acoustic neurinoma, astrocytomas such as piloid astrocytomas, fibrillary astrocytoma, protoplasmic astrocytoma, gemistocytic astrocytoma, anaplastic astrocytoma and glioblastomas, brain lymphomas, brain metastases, hypophyseal tumour such as prolactinoma, HGH (human growth hormone) producing tumour and ACTH-producing tumour (adrenocorticotrophic hormone), craniopharyngiomas, medulloblastomas, meningiomas and oligodendrogliomas; nerve tumours (neoplasms) such as tumours of the vegetative nervous system such as neuroblastoma sympathicum, ganglioneuroma, paraganglioma (phaeochromocytoma and chromaffinoma) and glomus caroticum tumour, tumours in the peripheral nervous system such as amputation neuroma, neurofibroma, neurinoma (neurilemoma, schwannoma) and malignant schwannoma, as well as tumours in the central nervous system such as brain and spinal cord tumours; intestinal cancer such as rectal carcinoma, colon carcinoma, anal carcinoma, small intestine tumours and duodenal tumours; eyelid tumours such as basalioma or basal cell carcinoma; pancreatic gland cancer or pancreatic carcinoma; bladder cancer or bladder carcinoma; lung cancer (bronchial carcinoma) such as small-cell bronchial carcinomas (oat cell carcinomas) and non-small-cell bronchial carcinomas such as squamous epithelium carcinomas, adenocarcinomas and large-cell bronchial carcinomas; breast cancer such as mammary carcinoma, such as infiltrating ductal carcinoma, colloid carcinoma, lobular invasive carcinoma, tubular carcinoma, adenoid cystic carcinoma, and papillary carcinoma; non-Hodgkin's lymphomas (NHL) such as Burkitt's lymphoma, low-malignancy non-Hodgkin's lymphomas (NHL) and mucosis fungoides; uterine cancer or endometrial carcinoma or corpus carcinoma; CUP syndrome (cancer of unknown primary); ovarian cancer or ovarian carcinoma such as mucinous, endometrial or serous cancer; gall bladder cancer; bile duct cancer such as Klatskin's tumour; testicular cancer such as seminomas and non-seminomas; lymphoma (lymphosarcoma) such as malignant lymphoma, Hodgkin's disease, non-Hodgkin's lymphomas (NHL) such as chronic lymphatic leukaemia, hair cell leukaemia, immunocytoma, plasmocytoma (multiple myeloma), immunoblastoma, Burkitt's lymphoma, T-zone mycosis fungoides, large-cell anaplastic lymphoblastoma and lymphoblastoma; laryngeal cancer such as vocal cord tumours,

supraglottal, glottal and subglottal laryngeal tumours; bone cancer such as osteochondroma, chondroma, chondroblastoma, chondromyxoidfibroma, osteoma, osteoid-osteoma, osteoblastoma, eosinophilic granuloma, giant cell tumour, chondrosarcoma, osteosarcoma, Ewing's sarcoma, reticulosarcoma, plasmocytoma, fibrous dysplasia, juvenile bone cyst and aneurysmatic bone cyst; head/neck tumours such as tumours of the lips, tongue, floor of the mouth, oral cavity, gingiva, pallet, salivary glands, pharynx, nasal cavities, paranasal sinuses, larynx and middle ear; liver cancer such as liver cell carcinoma or hepatocellular carcinoma (HCC); leukaemias, such as acute leukaemias, such as acute lymphatic/lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML); chronic leukaemias such as chronic lymphatic leukaemia (CLL), chronic myeloid leukaemia (CML); stomach cancer or stomach carcinoma such as papillary, tubular and mucinous adenocarcinoma, signet ring cell carcinoma, adenoid squamous cell carcinoma, small-cell carcinoma and undifferentiated carcinoma; melanomas such as superficially spreading, nodular malignant lentigo and acral lentiginous melanoma; renal cancer, such as kidney cell carcinoma or hypernephroma or Grawitz's tumour; oesophageal cancer or oesophageal carcinoma; cancer of the penis; prostate cancer; pharyngeal cancer or pharyngeal carcinomas such as nasopharyngeal carcinomas, oropharyngeal carcinomas and hypopharyngeal carcinomas; retinoblastoma; vaginal cancer or vaginal carcinoma; squamous epithelium carcinomas, adeno carcinomas, in situ carcinomas, malignant melanomas and sarcomas; thyroid gland carcinomas such as papillary, follicular and medullary thyroid gland carcinoma, and also anaplastic carcinomas; spinalioma, prickle cell carcinoma and squamous epithelium carcinoma of the skin; thymomas, urethral cancer and vulvar cancer.

The novel compounds can be used for the prevention or short-term or long-term treatment of the abovementioned diseases including, where appropriate, in combination with other state-of-the-art compounds such as other anti-tumour substances, cytotoxic substances, cell proliferation inhibitors, antiangiogenic substances, steroids or antibodies.

The compounds of the general formula (1) can be used on their own or in combination with other active compounds according to the invention and, where appropriate, in combination with other pharmacologically active compounds as well. Chemotherapeutic

agents which can be administered in combination with the compounds according to the invention include, without being restricted thereto, hormones, hormone analogs and antihormones (e.g. tamoxifen, toremifene, raloxifene, fulvestrant, megestrol acetate, flutamide, nilutamide, bicalutamide, aminoglutethimide, cyproterone acetate, finasteride, 5 buserelin acetate, fludrocortisone, fluoxymesterone, medroxyprogesterone and octreotide), aromatase inhibitors (e.g. anastrozole, letrozole, liarozole, vorozole, exemestane and atamestane), LHRH agonists and antagonists (e.g. goserelin acetate and luprolide), inhibitors of growth factors (growth factors such as platelet-derived growth factor and hepatocyte growth factor, examples of inhibitors are growth factor antibodies, 10 growth factor receptor antibodies and tyrosine kinase inhibitors, such as gefitinib, imatinib, lapatinib, Erbitux® and trastuzumab); antimetabolites (e.g. antifolates such as methotrexate and raltitrexed, pyrimidine analogs such as 5-fluorouracil, capecitabine and gemcitabine, purine and adenosine analogs such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine and fludarabine); antitumour antibiotics (e.g. 15 anthracyclines, such as doxorubicin, daunorubicin, epirubicin and idarubicin, mitomycin C, bleomycin, dactinomycin, plicamycin and streptozocin); platinum derivatives (e.g. cisplatin, oxaliplatin and carboplatin); alkylating agents (e.g. estramustine, mecllorethamine, melphalan, chlorambucil, busulphan, dacarbazine, cyclophosphamide, ifosfamide and temozolomide, nitrosoureas such as carmustine and lomustine and 20 thiotepa); antimitotic agents (e.g. vinca alkaloids such as vinblastine, vindesine, vinorelbine and vincristine; and taxans such as paclitaxel and docetaxel); topoisomerase inhibitors (e.g. epipodophyllotoxins such as etoposide and etopophos, teniposide, amsacrine, topotecan, irinotecan and mitoxantrone) and various chemotherapeutic agents such as amifostin, anagrelide, clodronate, filgrastin, interferon alpha, leucovorin, 25 rituximab, procarbazine, levamisole, mesna, mitotan, pamidronate and porfimer.

Examples of suitable forms for use are tablets, capsules, suppositories, solutions, in particular solutions for injection (s.c., i.v., i.m.) and infusion, syrups, emulsions or dispersible powders. In this connection, the proportion of the pharmaceutically active compound(s) should in each case be in the range of 0.1-90% by weight, preferably 30 0.5 - 50 % by weight, of the total composition, that is in quantities which are sufficient to

achieve the dosage range which is specified below. If necessary, the doses mentioned can be given several times a day.

Appropriate tablets can be obtained, for example, by mixing the active compound(s) with known auxiliary substances, for example inert diluents, such as calcium carbonate,
5 calcium phosphate or lactose, disintegrants, such as maize starch or alginic acid, binders, such as starch or gelatine, lubricants, such as magnesium stearate or talc, and/or agents for achieving a depot effect, such as carboxymethyl cellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets can also comprise several layers.

Correspondingly, sugar-coated tablets can be produced by coating cores, which have been
10 prepared in analogy with tablets, with agents which are customarily used in sugar coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. The core can also comprise several layers in order to achieve a depot effect or to avoid incompatibilities. In the same way, the sugar coating can also comprise several layers in order to achieve a depot effect, with it being possible to use the auxiliary substances
15 which are mentioned above in the case of the tablets.

Syrups of the active compounds or active compound combinations according to the invention can additionally comprise a sweetening agent, such as saccharine, cyclamate, glycerol or sugar as well as a taste-improving agent, e.g. flavouring agents such as vanillin or orange extract. They can also comprise suspension aids or thickeners, such as
20 sodium carboxymethyl cellulose, wetting agents, for example condensation products of fatty alcohols and ethylene oxide, or protectants such as p-hydroxybenzoates.

Injection and infusion solutions are produced in a customary manner, e.g. while adding isotonizing agents, preservatives, such as p-hydroxybenzoates, or stabilizers, such as alkali metal salts of ethylenediaminetetraacetic acid, where appropriate using emulsifiers
25 and/or dispersants, with it being possible, for example, to employ, where appropriate, organic solvents as solubilizing agents or auxiliary solvents when using water as diluent, and aliquoted into injection bottles or ampoules or infusion bottles.

The capsules, which comprise one or more active compounds or active compound

combinations, can, for example, be produced by mixing the active compounds with inert carriers, such as lactose or sorbitol, and encapsulating the mixture in gelatine capsules. Suitable suppositories can be produced, for example, by mixing with excipients which are envisaged for this purpose, such as neutral fats or polyethylene glycol, or their
5 derivatives.

Auxiliary substances which may be mentioned by way of example are water, pharmaceutically unobjectionable organic solvents, such as paraffins (e.g. petroleum fractions), oils of vegetable origin (e.g. groundnut oil or sesame oil), monofunctional or polyfunctional alcohols (e.g. EtOH or glycerol), carrier substances such as natural
10 mineral powders (e.g. kaolins, argillaceous earths, talc and chalk), synthetic mineral powders (e.g. highly disperse silicic acid and silicates), sugars (e.g. cane sugar, lactose and grape sugar), emulsifiers (e.g. lignin, sulphite waste liquors, methyl cellulose, starch and polyvinylpyrrolidone) and glidants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

15 Administration is effected in a customary manner, preferably orally or transdermally, in particular and preferably orally. In the case of oral use, the tablets can naturally also comprise, in addition to the abovementioned carrier substances, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with a variety of further substances such as starch, preferably potato starch, gelatine and the like. It is furthermore
20 also possible to use glidants, such as magnesium stearate, sodium lauryl sulphate and talc, for the tableting. In the case of aqueous suspensions, a variety of taste improvers or dyes can also be added to the active compounds in addition to the abovementioned auxiliary substances.

For parenteral administration, it is possible to employ solutions of the active compounds
25 while using suitable liquid carrier materials. The dosage for intravenous administration is 1-1000 mg per hour, preferably between 5 and 500 mg per hour.

Despite this, it may be necessary, where appropriate, to diverge from the abovementioned quantities, depending on the body weight or the nature of the route of administration, on the individual response to the medicament, on the nature of its formulation and on the

time or interval at which the administration is effected. Thus, it may, in some cases, be sufficient to make do with less than the previously mentioned lowest quantity whereas, in other cases, the abovementioned upper limit has to be exceeded. When relatively large quantities are being administered, it may be advisable to divide these into several single
 5 doses which are given over the course of the day.

The following formulation examples illustrate the present invention without, however, restricting its scope:

Pharmaceutical formulation examples

A) Tablets	per tablet
10 Active compound in accordance with formula (1)	100 mg
Lactose	140 mg
Maize starch	240 mg
Polyvinylpyrrolidone	15 mg
Magnesium stearate	<u>5 mg</u>
15	500 mg

The finely ground active compound, lactose and a part of the maize starch are mixed with each other. The mixture is sieved, after which it is moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granular material,
 20 the remainder of the maize starch and the magnesium stearate are sieved and mixed with each other. The mixture is pressed into tablets of suitable shape and size.

B) Tablets	per tablet
Active compound in accordance with formula (1)	80 mg
Lactose	55 mg
25 Maize starch	190 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	15 mg
Sodium carboxymethyl starch	23 mg

Magnesium stearate	<u>2 mg</u>
	400 mg

The finely ground active compound, a part of the maize starch, the lactose,
 5 microcrystalline cellulose and polyvinylpyrrolidone are mixed with each other, after
 which the mixture is sieved and worked, together with the remainder of the maize starch
 and water, into a granular material, which is dried and sieved. The sodium carboxymethyl
 starch and the magnesium stearate are then added to the granular material and mixed with
 it, and the mixture is pressed into tablets of suitable size.

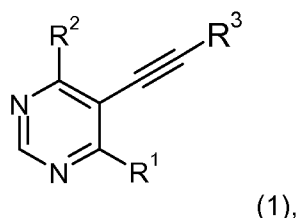
10 C) Ampoule solution

Active compound in accordance with formula (1)	50 mg
Sodium chloride	50 mg
Water for injection	5 mL

The active compound is dissolved, either at its intrinsic pH or, where appropriate, at
 15 pH 5.5-6.5, in water after which sodium chloride is added as isotonicizing agent. The
 resulting solution is rendered pyrogen-free by filtration and the filtrate is aliquoted, under
 aseptic conditions, into ampoules, which are then sterilized and sealed by melting. The
 ampoules contain 5 mg, 25 mg and 50 mg of active compound.

Claims

1. Compounds of general formula (1),



5

wherein

R³ denotes a group selected from among C₃₋₈cycloalkyl, 3-8 membered heterocycloalkyl, C₆₋₁₀aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different R⁴; and

10 **R¹** denotes a group selected from among C₃₋₈cycloalkyl, 3-13 membered heterocycloalkyl, and 2-6 membered heteroalkyl, optionally substituted by one or more identical or different R⁵ and

R² denotes a group selected from among hydrogen, C₁₋₄alkyl, 3-8 membered heteroalkyl, C₁₋₄haloalkyl, C₃₋₈cycloalkyl, 3-8 membered heterocycloalkyl, -OR^v,
15 -NR^vR^{v'}, -SR^v, -CF₃, -CHF₂, -CH₂F, -CN, -NC and -NO₂, and

each **R⁴** denotes a group selected from among R^a and R^b; and

each **R^a** independently denotes hydrogen or a group selected from among C₁₋₆alkyl, 2-6 membered heteroalkyl, C₁₋₆haloalkyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl,
20 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl, wherein R^a is optionally substituted by one or more identical or different **R^b** and/or **R^{c4}**;

each **R^b** denotes a suitable group and is selected independently of one another from among -OR^{c41}, C₁₋₃haloalkyloxy, -OCF₃, -OCHF₂, -SR^{c41}, -NR^{c41}R^{c42},
-ONR^{c41}R^{c42}, -N(OR^{c41})R^{c42}, -N(R^g)NR^{c41}R^{c42}, halogen, -CF₃, -CHF₂, -CH₂F, -CN,
25 -NC, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, and

each **R⁴**, **R^{c41}** and **R^{c42}** independently of one another denotes hydrogen or a group

selected from among C₁₋₆alkyl, 2-6 membered heteroalkyl, C₁₋₆haloalkyl,
 C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 5-12 membered
 hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and
 4-14 membered heterocycloalkylalkyl, wherein **R^{e41}** and **R^{e42}** independently
 5 optionally being substituted by one or more identical or different **R^d** and/or **R^{e4}**, and
 where **R^{e41}** and **R^{e42}** taken together may form a 3-8 membered heterocyclalkyl
 residue via a shared C-, N- O- or S-atom, and
 each **R^d** denotes a suitable group and is selected independently of one another from
 among -OR^{e41}, C₁₋₃haloalkyloxy, -OCF₃, -OCHF₂, -SR^{e41}, -NR^{e41}R^{e42},
 10 -ONR^{e41}R^{e42}, -N(R^g)NR^{e41}R^{e42}, halogen, -CF₃, -CN, -NC, -OCN, -SCN, -NO,
 -NO₂, =N₂, -N₃ and
 each **R^{e4}**, **R^{e41}** and **R^{e42}** independently of one another denotes hydrogen or a group
 selected from among C₁₋₆alkyl, 2-6 membered heteroalkyl, C₁₋₆haloalkyl,
 C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 5-12 membered
 15 hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and
 4-14 membered heterocycloalkylalkyl, wherein **R^{e41}** and **R^{e42}** are optionally
 independently substituted by one or more identical or different **R^f** and/or **R^{g4}**, and
 where **R^{e41}** and/or **R^{e42}** taken together may form a 3-8 membered heterocyclalkyl
 residue via a shared C-, N- O- or S-atom and
 20 each **R^f** denotes a suitable group and in each case is selected independently of one
 another from among =O, -OR^{g41}, C₁₋₃haloalkyloxy, -OCF₃, -OCHF₂, =S, -SR^{g41},
 =NR^{g41}, =NOR^{g41}, =NNR^{g41}R^{g42}, =NN(R^h)C(O)NR^{g41}R^{g42}, -NR^{g41}R^{g42},
 -ONR^{g41}R^{g42}, -N(R^h)NR^{g41}R^{g42}, halogen, -CF₃, -CN, -NC, -OCN, -SCN, -NO,
 -NO₂, =N₂, -N₃, -S(O)R^{g41}, -S(O)OR^{g41}, -S(O)₂R^{g41}, -S(O)₂OR^{g41}, -S(O)NR^{g41}R^{g42},
 25 -S(O)₂NR^{g41}R^{g42}, -OS(O)R^{g41}, -OS(O)₂R^{g41}, -OS(O)₂OR^{g41}, -OS(O)NR^{g41}R^{g42},
 -OS(O)₂NR^{g41}R^{g42}, -C(O)R^{g41}, -C(O)OR^{g41}, -C(O)SR^{g41}, -C(O)NR^{g41}R^{g42},
 -C(O)N(R^h)NR^{g41}R^{g42}, -C(O)N(R^h)OR^{g41}, -C(NR^h)NR^{g41}R^{g42}, -C(NOH)R^{g41},
 -C(NOH)NR^{g41}R^{g42}, -OC(O)R^{g41}, -OC(O)OR^{g41}, -OC(O)SR^{g41}, -OC(O)NR^{g41}R^{g42},
 -OC(NR^h)NR^{g41}R^{g42}, -SC(O)R^{g41}, -SC(O)OR^{g41}, -SC(O)NR^{g41}R^{g42},
 30 -SC(NR^h)NR^{g41}R^{g42}, -N(R^h)C(O)R^{g41}, -N[C(O)R^{g41}]₂, -N(OR^h)C(O)R^{g41},
 -N(R^h)C(NR^{h'})R^{g41}, -N(R^h)N(R^{h'})C(O)R^{g41}, -N[C(O)R^{g43}]NR^{g41}R^{g42},

$-N(R^h)C(S)R^{g41}$, $-N(R^h)S(O)R^{g41}$, $-N(R^h)S(O)OR^{g41}$, $-N(R^h)S(O)_2R^{g41}$,
 $-N[S(O)_2R^{g41}][S(O)_2R^{g42}]$, $-N(R^h)S(O)_2OR^{g41}$, $-N(R^h)S(O)_2NR^{g41}R^{g42}$,
 $-N(R^h)[S(O)_2]_2R^{g41}$, $-N(R^h)C(O)OR^{g41}$, $-N(R^h)C(O)SR^{g41}$, $-N(R^h)C(O)NR^{g41}R^{g42}$,
 $-N(R^h)C(O)NR^{h'}NR^{g41}R^{g42}$, $-N(R^h)N(R^{h'})C(O)NR^{g41}R^{g42}$, $-N(R^h)C(S)NR^{g41}R^{g42}$,
5 $-[N(R^h)C(O)][N(R^{h'})C(O)]R^{g41}$, $-N(R^h)[C(O)]_2R^{g41}$, $-N\{[C(O)]_2R^{g41}\}\{[C(O)]_2R^{g42}\}$,
 $-N(R^h)[C(O)]_2OR^{g41}$, $-N(R^h)[C(O)]_2NR^{g41}R^{g42}$, $-N\{[C(O)]_2OR^{g41}\}\{[C(O)]_2OR^{g41}\}$,
 $-N\{[C(O)]_2NR^{g41}R^{g42}\}\{[C(O)]_2NR^{g41}R^{g42}\}$, $-[N(R^h)C(O)][N(R^{h'})C(O)]OR^{g41}$,
 $-N(R^h)C(NR^{h'})OR^{g41}$, $-N(R^h)C(NOHR^{g41})R^{g41}$, $-N(R^h)C(NR^{h'})SR^{g41}$,
 $-N(R^h)C(NR^{h'})NR^{g41}R^{g42}$; and $-N=C(R^h)NR^{g41}R^{g42}$; and
10 each R^{g4} , R^{g41} , R^{g42} and R^{g43} independently of one another denotes hydrogen or a
group selected from among C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl,
 C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered
hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and
4-14 membered heterocycloalkylalkyl, where R^{g41} and/or R^{g42} and/or R^{g43} taken
15 together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N- O- or
S-atom, wherein each R^{g41} , R^{g42} and R^{g43} is optionally independently substituted by
one or more identical or different $R^{h''}$; and
each R^h , $R^{h'}$ and $R^{h''}$ is selected independently of one another from among hydrogen,
 C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl,
20 C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered heteroaryl,
6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14
membered heterocycloalkylalkyl, where R^h and $R^{h'}$ taken together may form a 3-8
membered heterocyclalkyl residue via a shared C-, N-, O- or S-atom, and
each R^5 denotes a group selected from among R^{a5} and/or R^{b5} ,
25 each R^{a5} independently of one another denotes hydrogen or a group selected from
among C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl,
 C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered heteroaryl,
6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl, and
4-14 membered heterocycloalkylalkyl, wherein R^{a5} optionally being substituted by
30 one or more identical or different R^{b5} and/or R^{c51} ; and
each R^{b5} denotes a suitable group and is selected independently of one another from

among =O, -OR^{c5}, C₁₋₃haloalkyloxy, -OCF₃, -OCHF₂, =S, -SR^{c5}, =NR^{c5}, =NOR^{c5},
 =NNR^{c5}R^{c55}, =NN(R^{g5})C(O)NR^{c5}R^{c55}, -NR^{c5}R^{c55}, -ONR^{c5}R^{c55}, -N(OR^{c5})R^{c55},
 -N(R^{g5})NR^{c5}R^{c55}, halogen, -CF₃, -CHF₂, -CH₂F, -CN, -NC, -OCN, -SCN, -NO,
 -NO₂, =N₂, -N₃, -S(O)R^{c5}, -S(O)OR^{c5}, -S(O)₂R^{c5}, -S(O)₂OR^{c5}, -S(O)NR^{c5}R^{c55},
 5 -S(O)₂NR^{c5}R^{c55}, -OS(O)R^{c5}, -OS(O)₂R^{c5}, -OS(O)₂OR^{c5}, -OS(O)NR^{c5}R^{c55},
 -OS(O)₂NR^{c5}R^{c55}, -C(O)R^{c5}, -C(O)OR^{c5}, -C(O)SR^{c5}, -C(O)NR^{c5}R^{c55},
 -C(O)N(R^{g5})NR^{c5}R^{c55}, -C(O)N(R^{g5})OR^{c5}, -C(NR^{g5})NR^{c5}R^{c55}, -C(NOH)R^{c5},
 -C(NOH)NR^{c5}R^{c55}, -OC(O)R^{c5}, -OC(O)OR^{c5}, -OC(O)SR^{c5}, -OC(O)NR^{c5}R^{c55},
 -OC(NR^{g5})NR^{c5}R^{c55}, -SC(O)R^{c5}, -SC(O)OR^{c5}, -SC(O)NR^{c5}R^{c55},
 10 -SC(NR^{g5})NR^{c5}R^{c55}, -N(R^{g5})C(O)R^{c5}, -N[C(O)R^{c5}]₂, -N(OR^{g5})C(O)R^{c5},
 -N(R^{g5})C(NR^{g5})R^{c5}, -N(R^{g5})N(R^{g55})C(O)R^{c5}, -N[C(O)R^{c5}]NR^{c55}R^{c555},
 -N(R^{g5})C(S)R^{c5}, -N(R^{g5})S(O)R^{c5}, -N(R^{g5})S(O)OR^{c5}, -N(R^{g5})S(O)₂R^{c5},
 -N[S(O)₂R^{c5}]₂, -N(R^{g5})S(O)₂OR^{c5}, -N(R^{g5})S(O)₂NR^{c5}R^{c55}, -N(R^{g5})[S(O)₂]₂R^{c5},
 -N(R^{g5})C(O)OR^{c5}, -N(R^{g5})C(O)SR^{c5}, -N(R^{g5})C(O)NR^{c5}R^{c55},
 15 -N(R^{g5})C(O)NR^{g55}NR^{c5}R^{c55}, -N(R^{g5})N(R^{g55})C(O)NR^{c5}R^{c55}, -N(R^{g5})C(S)NR^{c5}R^{c55},
 -[N(R^{g5})C(O)]₂R^{c5}, -N(R^{g5})[C(O)]₂R^{c5}, -N{[C(O)]₂R^{c5}}₂, -N(R^{g5})[C(O)]₂OR^{c5},
 -N(R^{g5})[C(O)]₂NR^{c5}R^{c55}, -N{[C(O)]₂OR^{c5}}₂, -N{[C(O)]₂NR^{c5}R^{c55}}₂,
 -[N(R^{g5})C(O)]₂OR^{c5}, -N(R^{g5})C(NR^{g55})OR^{c5}, -N(R^{g5})C(NOH)R^{c5},
 -N(R^{g5})C(NR^{g55})SR^{c5}, -N(R^{g5})C(NR^{g55})NR^{c5}R^{c55} and -N=C(R^{g5})NR^{c5}R^{c55} where R^{c5}
 20 and/or R^{c55} and/or R^{c555} taken together may form a 3-8 membered heterocyclalkyl
 residue via a shared C-, N-, O- or S-atom; and
 each R^{c51}, R^{c5}, R^{c55} and R^{c555} independently of one another denotes hydrogen or a
 group selected from among C₁₋₆alkyl, 2-6 membered heteroalkyl, C₁₋₆haloalkyl,
 C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 5-12 membered
 25 hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and
 4-14 membered heterocycloalkylalkyl, wherein each R^{c51}, R^{c5}, R^{c55} and/or R^{c555}
 optionally being independently substituted by one or more identical or different R^{d5}
 and/or R^{e51}; and
 each R^{d5} denotes a suitable group and is selected independently of one another from
 30 among =O, -OR^{c5}, C₁₋₃haloalkyloxy, -OCF₃, -OCHF₂, =S, -SR^{c5}, =NR^{c5}, =NOR^{c5},
 =NNR^{c5}R^{c55}, =NN(R^{g5})C(O)NR^{c5}R^{c55}, -NR^{c5}R^{c55}, -ONR^{c5}R^{c55}, -N(R^{g5})NR^{c5}R^{c55},

halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CN}$, $-\text{NC}$, $-\text{OCN}$, $-\text{SCN}$, $-\text{NO}$, $-\text{NO}_2$, $=\text{N}_2$, $-\text{N}_3$,
 $-\text{S}(\text{O})\text{R}^{\text{e}5}$, $-\text{S}(\text{O})\text{OR}^{\text{e}5}$, $-\text{S}(\text{O})_2\text{R}^{\text{e}5}$, $-\text{S}(\text{O})_2\text{OR}^{\text{e}5}$, $-\text{S}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{S}(\text{O})_2\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,
 $-\text{OS}(\text{O})\text{R}^{\text{e}5}$, $-\text{OS}(\text{O})_2\text{R}^{\text{e}5}$, $-\text{OS}(\text{O})_2\text{OR}^{\text{e}5}$, $-\text{OS}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{OS}(\text{O})_2\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,
 $-\text{C}(\text{O})\text{R}^{\text{e}5}$, $-\text{C}(\text{O})\text{OR}^{\text{e}5}$, $-\text{C}(\text{O})\text{SR}^{\text{e}5}$, $-\text{C}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{g}5})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,
 5 $-\text{C}(\text{O})\text{N}(\text{R}^{\text{g}5})\text{OR}^{\text{e}5}$, $-\text{C}(\text{NR}^{\text{g}5})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{C}(\text{NOH})\text{R}^{\text{e}5}$, $-\text{C}(\text{NOH})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,
 $-\text{OC}(\text{O})\text{R}^{\text{e}5}$, $-\text{OC}(\text{O})\text{OR}^{\text{e}5}$, $-\text{OC}(\text{O})\text{SR}^{\text{e}5}$, $-\text{OC}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{OC}(\text{NR}^{\text{g}5})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,
 $-\text{SC}(\text{O})\text{R}^{\text{e}5}$, $-\text{SC}(\text{O})\text{OR}^{\text{e}5}$, $-\text{SC}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{SC}(\text{NR}^{\text{g}5})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{R}^{\text{e}5}$,
 $-\text{N}[\text{C}(\text{O})\text{R}^{\text{e}5}]_2$, $-\text{N}(\text{OR}^{\text{g}5})\text{C}(\text{O})\text{R}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NR}^{\text{g}55})\text{R}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{N}(\text{R}^{\text{g}55})\text{C}(\text{O})\text{R}^{\text{e}5}$,
 $-\text{N}[\text{C}(\text{O})\text{R}^{\text{e}5}]\text{NR}^{\text{e}55}\text{R}^{\text{e}555}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{S})\text{R}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})\text{R}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})\text{OR}^{\text{e}5}$
 10 $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})_2\text{R}^{\text{e}5}$, $-\text{N}[\text{S}(\text{O})_2\text{R}^{\text{e}5}]_2$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})_2\text{OR}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{S}(\text{O})_2\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,
 $-\text{N}(\text{R}^{\text{g}5})[\text{S}(\text{O})_2]_2\text{R}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{OR}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{SR}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,
 $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})\text{NR}^{\text{e}55}\text{NR}^{\text{e}5}\text{R}^{\text{e}555}$, $-\text{N}(\text{R}^{\text{g}5})\text{N}(\text{R}^{\text{g}55})\text{C}(\text{O})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{S})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$,
 $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})_2\text{R}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})[\text{C}(\text{O})]_2\text{R}^{\text{e}5}$, $-\text{N}\{[\text{C}(\text{O})]_2\text{R}^{\text{e}5}\}_2$, $-\text{N}(\text{R}^{\text{g}5})[\text{C}(\text{O})]_2\text{OR}^{\text{e}5}$,
 $-\text{N}(\text{R}^{\text{g}5})[\text{C}(\text{O})]_2\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, $-\text{N}\{[\text{C}(\text{O})]_2\text{OR}^{\text{e}5}\}_2$, $-\text{N}\{[\text{C}(\text{O})]_2\text{NR}^{\text{e}5}\text{R}^{\text{e}55}\}_2$,
 15 $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{O})_2\text{OR}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NR}^{\text{g}55})\text{OR}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NOH})\text{R}^{\text{e}5}$,
 $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NR}^{\text{g}55})\text{SR}^{\text{e}5}$, $-\text{N}(\text{R}^{\text{g}5})\text{C}(\text{NR}^{\text{g}55})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$ and $-\text{N}=\text{C}(\text{R}^{\text{g}5})\text{NR}^{\text{e}5}\text{R}^{\text{e}55}$, where $\text{R}^{\text{e}5}$
 and/or $\text{R}^{\text{e}55}$ and/or $\text{R}^{\text{e}555}$ taken together may form a 3-8 membered heterocyclalkyl
 residue via a shared C-, N-, O- or S-atom; and
 each $\text{R}^{\text{e}51}$, $\text{R}^{\text{e}5}$, $\text{R}^{\text{e}55}$ and $\text{R}^{\text{e}555}$ independently of one another denotes hydrogen or a
 20 group selected from among C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl,
 C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered
 heteroaryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and
 4-14 membered heterocycloalkylalkyl wherein each $\text{R}^{\text{e}51}$, $\text{R}^{\text{e}5}$, $\text{R}^{\text{e}55}$ and/or $\text{R}^{\text{e}555}$
 optionally being independently substituted by one or more identical or different $\text{R}^{\text{f}5}$
 25 and/or $\text{R}^{\text{g}51}$; and
 each $\text{R}^{\text{f}5}$ denotes a suitable group and in each case is selected independently of one
 another from among $=\text{O}$, $-\text{OR}^{\text{g}52}$, C_{1-3} haloalkyloxy, $-\text{OCF}_3$, $-\text{OCHF}_2$, $=\text{S}$, $-\text{SR}^{\text{g}52}$,
 $=\text{NR}^{\text{g}52}$, $=\text{NOR}^{\text{g}52}$, $=\text{NNR}^{\text{g}52}\text{R}^{\text{g}53}$, $=\text{NN}(\text{R}^{\text{h}5})\text{C}(\text{O})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$,
 $-\text{ONR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{N}(\text{R}^{\text{h}5})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, halogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{CN}$, $-\text{NC}$, $-\text{OCN}$,
 30 $-\text{SCN}$, $-\text{NO}$, $-\text{NO}_2$, $=\text{N}_2$, $-\text{N}_3$, $-\text{S}(\text{O})\text{R}^{\text{g}52}$, $-\text{S}(\text{O})\text{OR}^{\text{g}52}$, $-\text{S}(\text{O})_2\text{R}^{\text{g}52}$, $-\text{S}(\text{O})_2\text{OR}^{\text{g}52}$,
 $-\text{S}(\text{O})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$,

$-\text{S}(\text{O})_2\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{OS}(\text{O})\text{R}^{\text{g}52}$, $-\text{OS}(\text{O})_2\text{R}^{\text{g}52}$, $-\text{OS}(\text{O})_2\text{OR}^{\text{g}52}$, $-\text{OS}(\text{O})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$,
 $-\text{OS}(\text{O})_2\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{C}(\text{O})\text{R}^{\text{g}52}$, $-\text{C}(\text{O})\text{OR}^{\text{g}52}$, $-\text{C}(\text{O})\text{SR}^{\text{g}52}$, $-\text{C}(\text{O})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$,
 $-\text{C}(\text{O})\text{N}(\text{R}^{\text{h}5})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{C}(\text{O})\text{N}(\text{R}^{\text{h}5})\text{OR}^{\text{g}52}$, $-\text{C}(\text{NR}^{\text{h}5})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{C}(\text{NOH})\text{R}^{\text{g}52}$,
 $-\text{C}(\text{NOH})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{OC}(\text{O})\text{R}^{\text{g}52}$, $-\text{OC}(\text{O})\text{OR}^{\text{g}52}$, $-\text{OC}(\text{O})\text{SR}^{\text{g}52}$, $-\text{OC}(\text{O})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$,
5 $-\text{OC}(\text{NR}^{\text{h}5})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{SC}(\text{O})\text{R}^{\text{g}52}$, $-\text{SC}(\text{O})\text{OR}^{\text{g}52}$, $-\text{SC}(\text{O})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$,
 $-\text{SC}(\text{NR}^{\text{h}5})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{O})\text{R}^{\text{g}52}$, $-\text{N}[\text{C}(\text{O})\text{R}^{\text{g}52}]_2$, $-\text{N}(\text{OR}^{\text{h}5})\text{C}(\text{O})\text{R}^{\text{g}52}$,
 $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{NR}^{\text{h}55})\text{R}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})\text{N}(\text{R}^{\text{h}55})\text{C}(\text{O})\text{R}^{\text{g}52}$, $-\text{N}[\text{C}(\text{O})\text{R}^{\text{g}52}]\text{NR}^{\text{g}53}\text{R}^{\text{g}54}$,
 $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{S})\text{R}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})\text{S}(\text{O})\text{R}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})\text{S}(\text{O})\text{OR}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})\text{S}(\text{O})_2\text{R}^{\text{g}52}$,
 $-\text{N}[\text{S}(\text{O})_2\text{R}^{\text{g}52}]_2$, $-\text{N}(\text{R}^{\text{h}5})\text{S}(\text{O})_2\text{OR}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})\text{S}(\text{O})_2\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{N}(\text{R}^{\text{h}5})[\text{S}(\text{O})_2]_2\text{R}^{\text{g}52}$,
10 $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{O})\text{OR}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{O})\text{SR}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{O})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$,
 $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{O})\text{NR}^{\text{h}55}\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{N}(\text{R}^{\text{h}5})\text{N}(\text{R}^{\text{h}55})\text{C}(\text{O})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$,
 $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{S})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{O})_2\text{R}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})[\text{C}(\text{O})]_2\text{R}^{\text{g}52}$, $-\text{N}\{[\text{C}(\text{O})]_2\text{R}^{\text{g}52}\}_2$,
 $-\text{N}(\text{R}^{\text{h}5})[\text{C}(\text{O})]_2\text{OR}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})[\text{C}(\text{O})]_2\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$, $-\text{N}\{[\text{C}(\text{O})]_2\text{OR}^{\text{g}52}\}_2$,
 $-\text{N}\{[\text{C}(\text{O})]_2\text{NR}^{\text{g}52}\text{R}^{\text{g}53}\}_2$, $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{O})_2\text{OR}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{NR}^{\text{h}55})\text{OR}^{\text{g}52}$,
15 $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{NOH})\text{R}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{NR}^{\text{h}55})\text{SR}^{\text{g}52}$, $-\text{N}(\text{R}^{\text{h}5})\text{C}(\text{NR}^{\text{h}55})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$; and
 $-\text{N}=\text{C}(\text{R}^{\text{h}5})\text{NR}^{\text{g}52}\text{R}^{\text{g}53}$; and

each $\text{R}^{\text{g}5}$, $\text{R}^{\text{g}51}$, $\text{R}^{\text{g}52}$, $\text{R}^{\text{g}53}$, $\text{R}^{\text{g}54}$ and $\text{R}^{\text{g}55}$ independently of one another denotes
hydrogen or a group selected from among C_{1-6} alkyl, 2-6 membered heteroalkyl,
 C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl,
20 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl, 3-14 membered
heterocycloalkyl and 4-14 membered heterocycloalkylalkyl wherein each $\text{R}^{\text{g}5}$, $\text{R}^{\text{g}51}$,
 $\text{R}^{\text{g}52}$, $\text{R}^{\text{g}53}$, $\text{R}^{\text{g}54}$ and $\text{R}^{\text{g}55}$ optionally being independently substituted by one or more
identical or different $\text{R}^{\text{h}51}$; and
each $\text{R}^{\text{h}51}$, $\text{R}^{\text{h}5}$, $\text{R}^{\text{h}55}$ and $\text{R}^{\text{h}555}$ is selected independently of one another from among
25 hydrogen, C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl,
 C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered heteroaryl,
6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14
membered heterocycloalkylalkyl; and
each R^{v} and $\text{R}^{\text{v}'}$ is selected independently of one another from among hydrogen,
30 C_{1-6} alkyl, 2-6 membered heteroalkyl, C_{1-6} haloalkyl,
optionally in the form of the prodrugs, the tautomers, the racemates, the enantiomers,

the diastereomers, the prodrugs and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

2. Compounds according to Claim 1, wherein **R**² denotes a group selected from among hydrogen, C₁₋₄alkyl, C₁₋₄haloalkyl, 3-8 membered heteroalkyl, C₃₋₈cycloalkyl,
 5 3-8 membered heterocycloalkyl, -OR^v, -NR^vR^{v'}, -CF₃, -CHF₂, -CH₂F, -CN, -NC and -NO₂; and
 each **R**^v and **R**^{v'} is selected independently of one another from among hydrogen, C₁₋₆alkyl, 2-6 membered heteroalkyl, C₁₋₆haloalkyl.
3. Compounds according to any of claim 1 to 2, wherein **R**² denotes -C₁₋₄-alkyl.
- 10 4. Compounds according to any of claims 1 to 3, wherein **R**² denotes -CH₃ or -C₂H₅.
5. Compounds according to any of claims 1 to 4, wherein **R**¹ denotes 3-13 membered heterocycloalkyl optionally substituted by one or more identical or different **R**⁵.
6. Compounds according to any of claims 1 to 5, wherein **R**¹ denotes 3-13 membered heterocycloalkyl comprising at least one nitrogen atom in the ring, wherein **R**¹ is
 15 optionally substituted by one or more identical or different **R**⁵ and wherein **R**¹ is attached to the pyrimidine ring in formula (1) via a nitrogen atom.
7. Compounds according claim 6, wherein **R**¹ denotes piperidine, piperazine, morpholine, pyrrolidine, homopiperazine, homomorpholine, thiomorpholine, 3,9-Diaza-spiro[5.5]undecane, 2,9-Diaza-spiro[5.5]undecane, 2,8-Diaza-
 20 spiro[4.5]decane, 1,8-Diaza-spiro[4.5]decane, 3-Aza-spiro[5.5]undecane, 1,5-Dioxa-9-aza-spiro[5.5]undecane, 2-Oxa-9-aza-spiro[5.5]undecane, 3-Oxa-9-aza-spiro[5.5]undecane, 8-Aza-spiro[4.5]decane, 2-Oxa-8-aza-spiro[4.5]decane, 1,4-Dioxa-8-aza-spiro[4.5]decane, 3-Aza-spiro[5.6]dodecane, 3,9-Diaza-spiro[5.6]dodecane, 9-Oxa-3-aza-spiro[5.6]dodecane or 1,3,8-Triaza-
 25 spiro[4.5]decane, wherein **R**¹ is optionally substituted by one or more identical or different **R**⁵ and wherein **R**¹ is attached to the pyrimidine ring in formula (1) via a nitrogen atom.

8. Compounds according to claim 7, wherein each R^5 independently of one another denotes a group selected from among R^{a5} and/or R^{b5} ; and each R^{a5} independently of one another denotes hydrogen or a group selected from among C_{1-4} alkyl, 2-6 membered heteroalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl, and 4-14 membered heterocycloalkylalkyl, wherein R^{a5} optionally being substituted by one or more identical or different R^{b5} and/or R^{c51} ; and
- each R^{b5} denotes a suitable group and is selected independently of one another from among $=O$, $-OR^{c5}$, $-OCF_3$, $-OCHF_2$, $=S$, $-NR^{c5}R^{c55}$, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CN$, $-S(O)R^{c5}$, $-S(O)_2R^{c5}$, $-S(O)_2NR^{c5}R^{c55}$, $-C(O)R^{c5}$, $-C(O)NR^{c5}R^{c55}$, $-C(O)N(R^{g5})OR^{c5}$, $-OC(O)NR^{c5}R^{c55}$, $-N(R^{g5})C(O)R^{c5}$, $-N(R^{g5})S(O)_2R^{c5}$, $-N(R^{g5})C(O)OR^{c5}$, $-N(R^{g5})C(O)NR^{c5}R^{c55}$, where R^{c5} and R^{c55} taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N-, O- or S-atom; and
- each R^{c51} , R^{c5} and R^{c55} independently of one another denotes hydrogen or a group selected from among C_{1-3} alkyl, 2-4 membered heteroalkyl, C_{1-2} haloalkyl, C_{3-7} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 6-12 membered heteroarylalkyl, 3-10 membered heterocycloalkyl and 4-10 membered heterocycloalkylalkyl, wherein R^{c51} , R^{c5} and/or R^{c55} independently optionally being substituted by one or more identical or different R^{d5} and/or R^{e51} ; and
- each R^{d5} denotes a suitable group and is selected independently of one another from among $=O$, $-OH$, $-OCH_3$, $-OC_2H_5$, $-OiPr$, $-OnPr$, $-OnBu$, $-OiBu$, $-OsecBu$, $-OtBu$, $-OCF_3$, $-OCHF_2$, $-NR^{e5}R^{e55}$, halogen, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CN$, where R^{e5} and R^{e55} taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N-, O- or S-atom; and
- each R^{e51} , R^{e5} and R^{e55} independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, methoxymethyl, ethoxymethyl, methoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, phenyl, benzyl, pyridyl, morpholine, piperidine, pyrrolidine, piperazine, tetrahydrofuryl and tetrahydropyranyl, wherein R^{e51} , R^{e5} and/or R^{e55} independently optionally being substituted by one or more

- identical or different R^{f5} and/or R^{g51} ; and
 each R^{f5} denotes a suitable group and in each case is selected independently of one another from among =O, -OH, -OCH₃, -OC₂H₅, -OCF₃, -OCHF₂, halogen, -CF₃, -CHF₂, -CN and
 5 each R^{g51} independently of one another denotes hydrogen or a group selected from among C₁₋₄alkyl, 2-6 membered heteroalkyl, C₃₋₈cycloalkyl, 3-10 membered heterocycloalkyl, C₆₋₁₀aryl and 5-12 membered heteroaryl, wherein R^{g51} optionally being substituted by one or more identical or different R^{h51} ; and
 each R^{h51} is selected independently of one another from among hydrogen, C₁₋₄alkyl,
 10 2-4 membered heteroalkyl, C₃₋₈cycloalkyl, C₆₋₁₀aryl, 5-8 membered heteroaryl, 3-10 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl.
9. Compounds according to any of claim 1 to 7, wherein R^1 denotes piperidine, piperazine, morpholine, 3,9-Diaza-spiro[5.5]undecane, 2,9-Diaza-spiro[5.5]undecane, 2,8-Diaza-spiro[4.5]decane, 1,8-Diaza-spiro[4.5]decane, 1,4-Dioxa-8-aza-spiro[4.5]decane, 3,9-Diaza-spiro[5.6]dodecane, wherein R^1 is
 15 optionally substituted by one or more identical or different R^5 and wherein R^1 is attached to the pyrimidine ring in formula (1) via a nitrogen atom and each R^5 independently of one another denotes a group selected from among R^{a5} and/or R^{b5} ; and
 20 each R^{a5} independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, methoxymethyl, ethoxymethyl, methoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, phenyl, benzyl, pyridyl, pyrimidinyl, morpholine, piperidine, pyrrolidine, piperazine, tetrahydrofuryl and tetrahydropyranyl, wherein
 25 R^{a5} optionally being substituted by one or more identical or different R^{b5} and/or R^{c51} ; and
 each R^{b5} denotes a suitable group and is selected independently of one another from among =O, -OH, -OCH₃, -OC₂H₅, -OCF₃, -OCHF₂, =S, -NR^{c5}R^{c55}, halogen, -CF₃, -CHF₂, -CH₂F, -CN, -S(O)₂R^{c5}, -S(O)₂NR^{c5}R^{c55}, -C(O)R^{c5}, -C(O)NR^{c5}R^{c55},
 30 -N(R^{g5})C(O)R^{c5}, -N(R^{g5})S(O)₂R^{c5}, -N(R^{g5})C(O)OR^{c5}, -N(R^{g5})C(O)NR^{c5}R^{c55}, where

- R^{c5} and R^{c55} taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N-, O- or S-atom; and
- each R^{c51} , R^{c5} and R^{c55} independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, methoxymethyl, ethoxymethyl, methoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, phenyl, benzyl, morpholine, piperidine, pyrrolidine, piperazine, tetrahydrofuryl, tetrahydropyranyl and 5-6 membered heteroaryl, wherein R^{c51} , R^{c5} and R^{c55} independently optionally being substituted by one or more identical or different R^{d5} and/or R^{e51} ; and
- each R^{d5} denotes a suitable group and is selected independently of one another from among =O, -OH, -OCH₃, -OC₂H₅, -OCF₃, -OCHF₂, -NR^{e5}R^{e55}, halogen, -CF₃, -CHF₂, -CH₂F, -CN, where R^{e5} and R^{e55} taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N-, O- or S-atom; and
- each R^{e51} , R^{e5} and R^{e55} independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, methoxymethyl, ethoxymethyl, methoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, phenyl, benzyl, pyridyl, morpholine, piperidine, pyrrolidine, piperazine, tetrahydrofuryl, tetrahydropyranyl; and
- each R^{g5} independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl, methoxymethyl, ethoxymethyl, methoxyethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, phenyl, benzyl, pyridyl, morpholine, piperidine, pyrrolidine, piperazine, tetrahydrofuryl, tetrahydropyranyl.
10. Compounds according to any of claims 1 to 9, wherein R^3 denotes C₆₋₁₀aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different R^4 ; and each R^4 denotes a group selected from among R^a and/or R^b ; and each R^a independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl and cyclopropyl, wherein R^a is optionally substituted by one or more identical or different R^b and/or R^{c4} ; and
- each R^b denotes a suitable group and is selected independently of one another from among -OH, -OCH₃, -OC₂H₅, -OCF₃, -OCHF₂, -NR^{c41}R^{c42}, halogen, -CF₃, -CHF₂,

- CH₂F, -CN, -NC, and
 each **R^{c4}**, **R^{c41}** and **R^{c42}** independently of one another denotes hydrogen or a group optionally substituted by one or more identical or different **R^d**, selected from among methyl, ethyl, prop-1-yl, prop-2-yl, *tert*-butyl, *sec*-butyl, butyl, *iso*-butyl,
 5 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, aminoethyl, aminopropyl, hydroxyethyl, methoxyethyl, phenyl and pyridyl wherein **R^{c4}**, **R^{c41}** and/or **R^{c42}** independently optionally being substituted by one or more identical or different **R^d**, and where **R^{c41}** and **R^{c42}** taken together may form a 3-8 membered heterocyclalkyl residue via a shared C-, N- O- or S-atom, and
 10 each **R^d** denotes a suitable group and is selected independently of one another from among -OH, -OCH₃, -OC₂H₅, -OiPr, -OnPr, -OCF₃, -OCHF₂, -NR^{e41}R^{e42}, halogen, -CF₃, -CHF₂, -CH₂F, -CN and
 each **R^{e41}** and **R^{e42}** independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-1-yl, prop-2-yl, *tert*-butyl, *sec*-butyl, butyl,
 15 *iso*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, aminoethyl, aminopropyl, hydroxyethyl, methoxyethyl, where **R^{e41}** and **R^{e42}** taken together may form a 5-6 membered heterocyclalkyl residue via a shared C-, N- O- or S-atom.
11. Compounds according to any of claims 1 to 10, wherein **R³** denotes C₆₋₁₀aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or
 20 different **R⁴**; and each **R⁴** denotes a group selected from among **R^a** and **R^b**; and each **R^a** independently of one another denotes hydrogen or a group selected from among methyl, ethyl, prop-2-yl, prop-1-yl, cyclopropyl, and
 each **R^b** denotes a suitable group and is selected independently of one another from among -OH, -OCH₃, -OC₂H₅, -OCF₃, -OCHF₂, -NH₂, NHCH₃, NHC₂H₅, halogen,
 25 -CF₃, -CHF₂, -CH₂F, -CN.
12. Compounds according to any of claims 1 to 11, wherein **R³** denotes 5-12 membered heteroaryl, optionally substituted by one or more identical or different **R⁴**.
13. Compounds according to any of claims 1 to 12, wherein **R³** denotes pyridyl, optionally substituted by one or more identical or different **R⁴**.

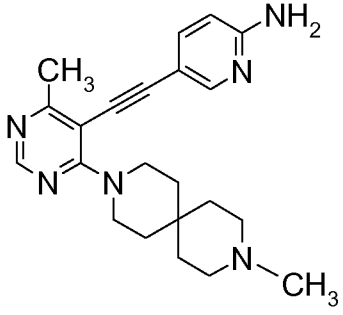
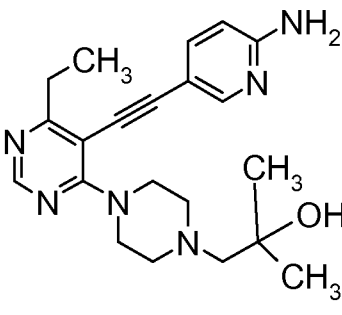
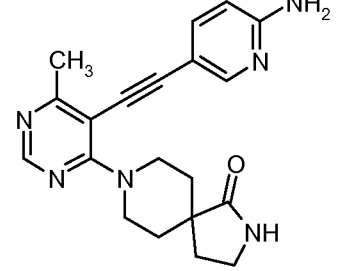
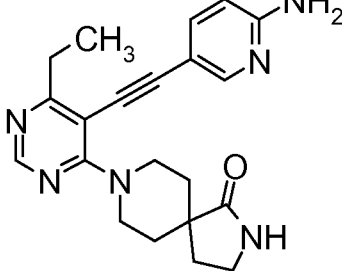
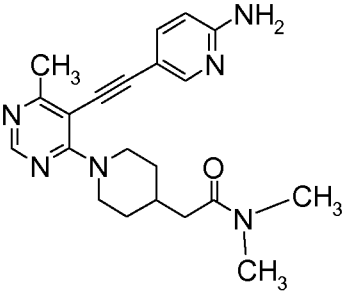
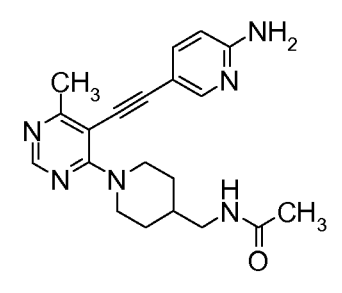
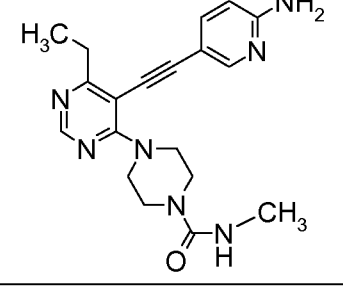
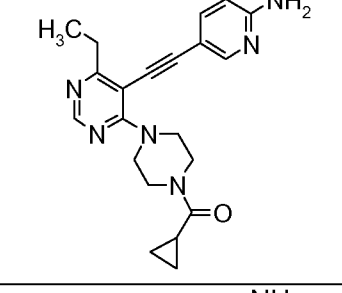
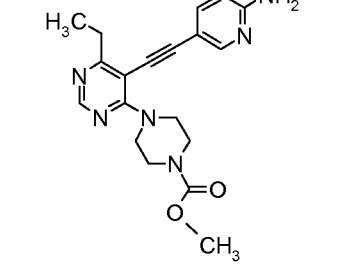
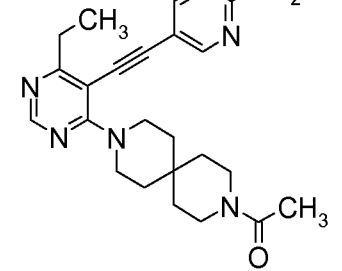
14. Compounds according to any of claims 1 to 11, wherein R^3 denotes phenyl and pyridyl optionally substituted by one or more identical or different R^4 ; and each R^4 denotes a group selected from among methyl, ethyl, $-NH_2$, $NHCH_3$, NHC_2H_5 .

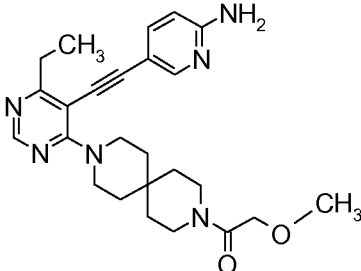
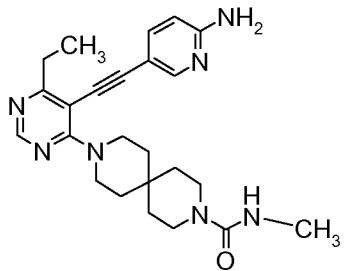
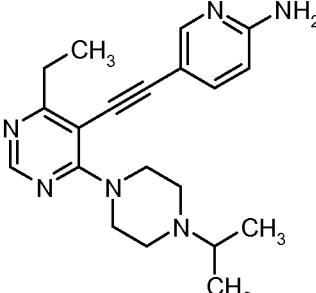
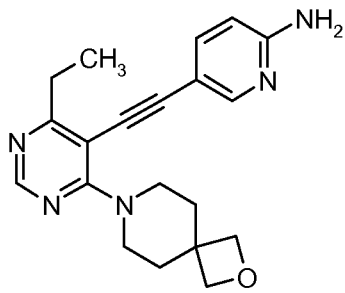
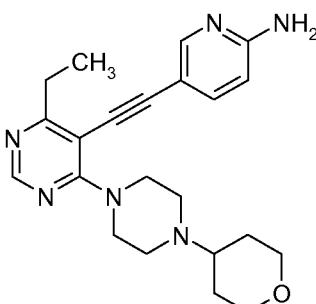
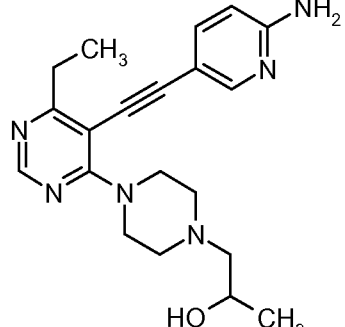
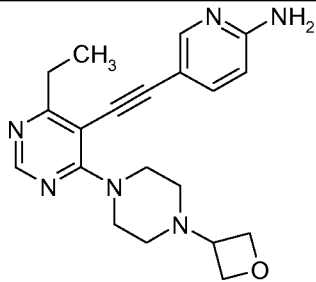
15. Compounds according to any of claims 1 to 14 selected from

Nr.	Structure	Nr.	Structure
B-2		B-4	
B-5		B-8	
B-11		B-13	
B-14		B-19	

Nr.	Structure	Nr.	Structure
B-23		B-31	
B-35		B-36	
B-38		B-40	
B-41		B-42	
B-44		B-47	

Nr.	Structure	Nr.	Structure
B-48		B-51	
B-52		B-53	
B-56		B-57	
B-63		B-66	
B-68		B-79	

Nr.	Structure	Nr.	Structure
B-80		B-81	
B-84		B-85	
E-1		F-1	
G-1		G-4	
G-6		G-11	

Nr.	Structure	Nr.	Structure
G-12		G-13	
H-6		H-7	
H-12		H-20	
H-26			

16. Compounds, or the pharmacologically effective salts thereof, according to any one of claims 1 to 15, as medicaments.

17. Compounds, or the pharmacologically effective salts thereof, according to any one of claims 1 to 15, for preparing a medicament with an antiproliferative activity.

18. Pharmaceutical preparations, containing as active substance one or more compounds of general formula (1) according to any one of claims 1 to 15 or the pharmacologically effective salts thereof, optionally in combination with conventional excipients and/or carriers.
- 5 19. Compounds of general formula (1) according to any one of claims 1 to 15 for use in the treatment and/or prevention of cancer, infections, inflammatory and autoimmune diseases.
20. Use of compounds of general formula (1) according to any one of claims 1 to 15 for preparing a medicament for the treatment and/or prevention of cancer, infections,
10 inflammatory and autoimmune diseases.
21. Pharmaceutical preparation comprising a compound of general formula (1) according to any one of claims 1 to 15 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
15 optionally the pharmacologically acceptable salts thereof.