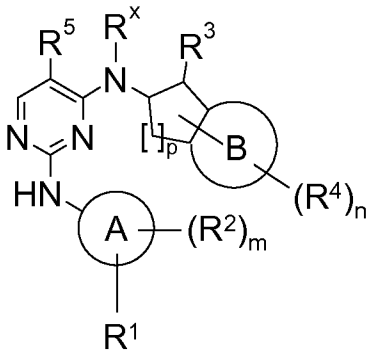
2, 4 -DIAMINO PYRIMIDINES FOR THE TREATMENT OF DISEASES CHARACTERISED BY EXCESSIVE OR ABNORMAL CELL PROLIFERATION

The present invention relates to new 2,4-diaminopyrimidines of general formula **(1)**



(1) ,

wherein the groups **A**, **B**, R^1 to R^5, R^x, **m**, **n** and **p** have the meanings given in the claims and specification, the isomers thereof, processes for preparing these pyrimidines and their use as medicaments.

Background to the invention

Tumour cells that acquire the properties for invasion and metastasisation require specific survival signals. These signals allow them to overcome special apoptosis mechanisms (anoikis) which are triggered, inter alia, by the loss of cell adhesion. In this process, focal adhesion kinase (FAK/PTK2) is one of the essential signal molecules which on the one hand controls cell-matrix interactions through so-called 'focal adhesions' and on the other hand imparts anoikis resistance. Interference with these mechanisms by inhibiting PTK2 may lead to the apoptotic cell death of tumour cells and limit the invasive and metastasising growth of tumours. In addition, focal adhesion kinase has major significance for the growth, migration and survival of tumour-associated endothelial cells. An anti-angiogenic activity may therefore also be achieved by inhibiting PTK2.

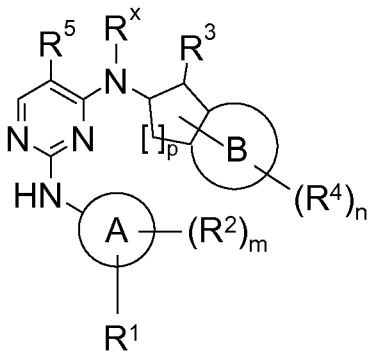
Pyrimidines are generally known as inhibitors of kinases. Thus, for example, 2,4,5-trisubstituted pyrimidines are described as active components with an anti-cancer activity in International Patent Applications WO 2003/030909 and WO 2003/032997, while most compounds in these patent specifications do not carry a substituent at the bicyclic ring in the 4-position of the pyrimidine.

The aim of the present invention is to indicate new diaminopyrimidines as active substances which can be used for the prevention and/or treatment of diseases characterised by excessive or abnormal cell proliferation. A further aim of the present invention is to indicate diaminopyrimidines which have an inhibitory effect on the enzyme PTK2 *in vitro* and/or *in vivo* and have suitable pharmacological and/or pharmacokinetic properties to enable them to be used as medicaments. These properties include inter alia a selective inhibitory effect on PTK2 in relation to other known cell cycle and signal kinases.

Detailed description of the invention

It has been found that, surprisingly, compounds of general formula **(1)**, wherein the groups **A**, **B**, $\mathbf{R^1}$ to $\mathbf{R^5}$, $\mathbf{R^x}$, **m**, **n** and **p** have the meanings given below, act as specific inhibitors against PTK2. Thus, the compounds according to the invention may be used for example for treating diseases connected with the activity of PTK2 and characterised by excessive or abnormal cell proliferation.

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



(1) , wherein

A is a group selected from among C_{6-15}aryl and 5-12 membered heteroaryl;

B is a group selected from among C_{6-10}aryl and 5-10 membered heteroaryl;

$\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^4}$ and $\mathbf{R^x}$ each independently of one another denote hydrogen or a group selected from among $\mathbf{R^a}$, $\mathbf{R^b}$ and $\mathbf{R^a}$ substituted by one or more, identical or different $\mathbf{R^c}$ and/or $\mathbf{R^b}$;

$\mathbf{R^3}$ is a group selected from among $-NR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, $-N(R^g)C(O)R^c$, $-N[C(O)R^c]_2$, $-N(OR^g)C(O)R^c$, $-N(R^g)C(NR^g)R^c$, $-N(R^g)N(R^g)C(O)R^c$, $-N[C(O)R^c]NR^cR^c$, $-N(R^g)C(S)R^c$, $-N(R^g)S(O)R^c$, $-N(R^g)S(O)OR^c$, $-N(R^g)S(O)_2R^c$, $-N[S(O)_2R^c]_2$,

$-N(R^g)S(O)_2OR^c$, $-N(R^g)S(O)_2NR^cR^c$, $-N(R^g)[S(O)_2]_2R^c$, $-N(R^g)C(O)OR^c$, $-N(R^g)C(O)SR^c$, $-N(R^g)C(O)NR^cR^c$, $-N(R^g)C(O)NR^gNR^cR^c$, $-N(R^g)N(R^g)C(O)NR^cR^c$, $-N(R^g)C(S)NR^cR^c$, $-[N(R^g)C(O)]_2R^c$, $-N(R^g)[C(O)]_2R^c$, $-N\{[C(O)]_2R^c\}_2$, $-N(R^g)[C(O)]_2OR^c$, $-N(R^g)[C(O)]_2NR^cR^c$, $-N\{[C(O)]_2OR^c\}_2$, $-N\{[C(O)]_2NR^cR^c\}_2$, $-[N(R^g)C(O)]_2OR^c$, $-N(R^g)C(NR^g)OR^c$, $-N(R^g)C(NOH)R^c$, $-N(R^g)C(NR^g)SR^c$ and $-N(R^g)C(NR^g)NR^cR^c$;

$\mathbf{R^5}$ is a group selected from among halogen, -CN, $-NO_2$, $-OR^c$, $-C(O)R^c$, $-NR^cR^c$, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl and 3-8 membered heterocycloalkyl;

each $\mathbf{R^a}$ is independently selected from among C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each $\mathbf{R^b}$ is a suitable group and is independently selected from among =O, $-OR^c$, C_{1-3}haloalkyloxy, $-OCF_3$, =S, $-SR^c$, $=NR^c$, $=NOR^c$, $=NNR^cR^c$, $=NN(R^g)C(O)NR^cR^c$, $-NR^cR^c$, $-ONR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^c$, $-S(O)OR^c$, $-S(O)_2R^c$, $-S(O)_2OR^c$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)_2OR^c$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)SR^c$, $-C(O)NR^cR^c$, $-C(O)N(R^g)NR^cR^c$, $-C(O)N(R^g)OR^c$, $-C(NR^g)NR^cR^c$, $-C(NOH)R^c$, $-C(NOH)NR^cR^c$, $-OC(O)R^c$, $-OC(O)OR^c$, $-OC(O)SR^c$, $-OC(O)NR^cR^c$, $-OC(NR^g)NR^cR^c$, $-SC(O)R^c$, $-SC(O)OR^c$, $-SC(O)NR^cR^c$, $-SC(NR^g)NR^cR^c$, $-N(R^g)C(O)R^c$, $-N[C(O)R^c]_2$, $-N(OR^g)C(O)R^c$, $-N(R^g)C(NR^g)R^c$, $-N(R^g)N(R^g)C(O)R^c$, $-N[C(O)R^c]NR^cR^c$, $-N(R^g)C(S)R^c$, $-N(R^g)S(O)R^c$, $-N(R^g)S(O)OR^c$, $-N(R^g)S(O)_2R^c$, $-N[S(O)_2R^c]_2$, $-N(R^g)S(O)_2OR^c$, $-N(R^g)S(O)_2NR^cR^c$, $-N(R^g)[S(O)_2]_2R^c$, $-N(R^g)C(O)OR^c$, $-N(R^g)C(O)SR^c$, $-N(R^g)C(O)NR^cR^c$, $-N(R^g)C(O)NR^gNR^cR^c$, $-N(R^g)N(R^g)C(O)NR^cR^c$, $-N(R^g)C(S)NR^cR^c$, $-[N(R^g)C(O)]_2R^c$, $-N(R^g)[C(O)]_2R^c$, $-N\{[C(O)]_2R^c\}_2$, $-N(R^g)[C(O)]_2OR^c$, $-N(R^g)[C(O)]_2NR^cR^c$, $-N\{[C(O)]_2OR^c\}_2$, $-N\{[C(O)]_2NR^cR^c\}_2$, $-[N(R^g)C(O)]_2OR^c$, $-N(R^g)C(NR^g)OR^c$, $-N(R^g)C(NOH)R^c$, $-N(R^g)C(NR^g)SR^c$ and $-N(R^g)C(NR^g)NR^cR^c$;

each $\mathbf{R^c}$ independently denotes hydrogen or a group optionally substituted by one or more, identical or different $\mathbf{R^d}$ and/or $\mathbf{R^e}$, selected from among C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{4-11}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^d** denotes a suitable group and is independently selected from among =O, -OR^e, C$_{1-3}$haloalkyloxy, -OCF$_3$, =S, -SR^e, =NR^e, =NOR^e, =NNR^{e}R^e, =NN(R^g)C(O)NR^{e}R^e, -NR^{e}R^e, -ONR^{e}R^e, -N(R^g)NR^{e}R^e, halogen, -CF$_3$, -CN, -NC, -OCN, -SCN, -NO, -NO$_2$, =N$_2$, -N$_3$, -S(O)R^e, -S(O)OR^e, -S(O)$_2$R^e, -S(O)$_2$OR^e, -S(O)NR^{e}R^e, -S(O)$_2$NR^{e}R^e, -OS(O)R^e, -OS(O)$_2$R^e, -OS(O)$_2$OR^e, -OS(O)NR^{e}R^e, -OS(O)$_2$NR^{e}R^e, -C(O)R^e, -C(O)OR^e, -C(O)SR^e, -C(O)NR^{e}R^e, -C(O)N(R^g)NR^{e}R^e, -C(O)N(R^g)OR^e, -C(NR^g)NR^{e}R^e, -C(NOH)R^e, -C(NOH)NR^{e}R^e, -OC(O)R^e, -OC(O)OR^e, -OC(O)SR^e, -OC(O)NR^{e}R^e, -OC(NR^g)NR^{e}R^e, -SC(O)R^e, -SC(O)OR^e, -SC(O)NR^{e}R^e, -SC(NR^g)NR^{e}R^e, -N(R^g)C(O)R^e, -N[C(O)R^e]$_2$, -N(OR^g)C(O)R^e, -N(R^g)C(NR^g)R^e, -N(R^g)N(R^g)C(O)R^e, -N[C(O)R^e]NR^{e}R^e, -N(R^g)C(S)R^e, -N(R^g)S(O)R^e, -N(R^g)S(O)OR^e, -N(R^g)S(O)$_2$R^e, -N[S(O)$_2$R^e]$_2$, -N(R^g)S(O)$_2$OR^e, -N(R^g)S(O)$_2$NR^{e}R^e, -N(R^g)[S(O)$_2$]$_2$R^e, -N(R^g)C(O)OR^e, -N(R^g)C(O)SR^e, -N(R^g)C(O)NR^{e}R^e, -N(R^g)C(O)NR^{g}NR^{e}R^e, -N(R^g)N(R^g)C(O)NR^{e}R^e, -N(R^g)C(S)NR^{e}R^e, -[N(R^g)C(O)]$_2$R^e, -N(R^g)[C(O)]$_2$R^e, -N{[C(O)]$_2$R^e}$_2$, -N(R^g)[C(O)]$_2$OR^e, -N(R^g)[C(O)]$_2$NR^{e}R^e, -N{[C(O)]$_2$OR^e}$_2$, -N{[C(O)]$_2$NR^{e}R^e}$_2$, -[N(R^g)C(O)]$_2$OR^e, -N(R^g)C(NR^g)OR^e, -N(R^g)C(NOH)R^e, -N(R^g)C(NR^g)SR^e and -N(R^g)C(NR^g)NR^{e}R^e;

each **R^e** independently denotes hydrogen or a group optionally substituted by one or more, identical or different **R^f** and/or **R^g**, selected from among C$_{1-6}$alkyl, C$_{3-8}$cycloalkyl, C$_{4-11}$cycloalkylalkyl, C$_{6-10}$aryl, C$_{7-16}$arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^f** denotes a suitable group and is independently selected from among halogen, -OR^g and -CF$_3$;

each **R^g** independently denotes hydrogen, C$_{1-6}$alkyl, C$_{3-8}$cycloalkyl, C$_{4-11}$cycloalkylalkyl, C$_{6-10}$aryl, C$_{7-16}$arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkyl, 5-12 membered heteroaryl or 6-18 membered heteroarylalkyl and

m is equal to 1, 2 or 3;

n is equal to 0, 1, 2, 3 or 4;

p is equal to 0, 1, 2 or 3;

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

In a preferred embodiment **(A1)** the present invention relates to compounds of general formula **(1)**, wherein

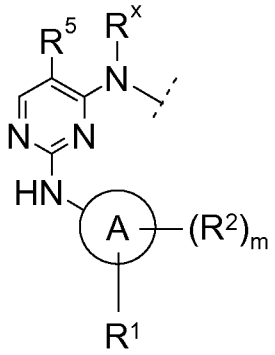
p is equal to 1 or 2.

In another preferred embodiment **(A2)** the present invention relates to compounds of general formula **(1)**, wherein

p is equal to 1.

In other preferred embodiments **(A3)** the present invention relates to compounds of the preferred embodiments **(A1)** and/or **(A2)**, wherein

the group $\mathbf{R^3}$ and the group



assume a *trans* configuration with respect to the ring system to which they are attached.

In another preferred embodiment **(B1)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^x}$ is hydrogen.

In another preferred embodiment **(C1)** the present invention relates to compounds of general formula **(1)**, wherein

B is phenyl or 5-6 membered heteroaryl and

$\mathbf{R^4}$ and **n** are as hereinbefore defined.

In another preferred embodiment **(C2)** the present invention relates to compounds of general formula **(1)**, wherein

B is phenyl or pyridyl and

$\mathbf{R^4}$ and **n** are as hereinbefore defined.

In another preferred embodiment **(C3)** the present invention relates to compounds of general formula **(1)**, wherein

B is phenyl and

$\mathbf{R^4}$ and **n** are defined as in claim 1.

In other preferred embodiments **(C4)** the present invention relates to compounds of the preferred embodiments **(C1)** and/or **(C2)** and/or **(C3)**, wherein

n has the value 0.

In another preferred embodiment **(D1)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^5}$ is a group selected from among halogen, $-CF_3$ and C_{1-4}haloalkyl.

In another preferred embodiment **(D2)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^5}$ is selected from among bromine, chlorine and $-CF_3$.

In another preferred embodiment **(D3)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^5}$ denotes $-CF_3$.

In another preferred embodiment **(D4)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^5}$ denotes chlorine.

In another preferred embodiment **(D5)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^5}$ denotes bromine.

In another preferred embodiment **(E1)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^3}$ is selected from among $-NR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, $-N(R^g)C(O)R^c$, $-N(OR^g)C(O)R^c$, $-N(R^g)N(R^g)C(O)R^c$, $-N(R^g)S(O)_2R^c$, $-N(R^g)C(O)OR^c$ and $-N(R^g)C(O)NR^cR^c$, and

$\mathbf{R^c}$ and $\mathbf{R^g}$ are as hereinbefore defined.

In another preferred embodiment **(E2)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^3}$ is selected from among $-N(R^g)C(O)R^c$, $-N(R^g)C(O)OR^c$ and $-N(R^g)S(O)_2R^c$, and

$\mathbf{R^c}$ and $\mathbf{R^g}$ are as hereinbefore defined.

In another preferred embodiment **(E3)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^3}$ is selected from among $-N(R^g)C(O)R^{c1}$ and $-N(R^g)S(O)_2R^{c1}$;

$\mathbf{R^{c1}}$ corresponds to the group $\mathbf{R^c}$ and

$\mathbf{R^c}$ and $\mathbf{R^g}$ are as hereinbefore defined.

In another preferred embodiment **(E4)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^3}$ is selected from among $-NHC(O)R^{c1}$, $-N(C_{1\text{-}4}alkyl)C(O)R^{c1}$, $-NHS(O)_2R^{c1}$ and $-N(C_{1\text{-}4}alkyl)S(O)_2R^{c1}$;

$\mathbf{R^{c1}}$ corresponds to the group $\mathbf{R^c}$ and

$\mathbf{R^c}$ is as hereinbefore defined.

In another preferred embodiment **(E5)** the present invention relates to compounds of general formula **(1)**, wherein

$\mathbf{R^3}$ is selected from among $-NHC(O)R^{c1}$, $-N(Me)C(O)R^{c1}$, $-N(Et)C(O)R^{c1}$, $-N(i\text{Pr})C(O)R^{c1}$, $-N(n\text{Pr})C(O)R^{c1}$, $-NHS(O)_2R^{c1}$, $-N(Me)S(O)_2R^{c1}$, $-N(Et)S(O)_2R^{c1}$, $-N(i\text{Pr})S(O)_2R^{c1}$ and $-N(n\text{Pr})S(O)_2R^{c1}$;

$\mathbf{R^{c1}}$ corresponds to the group $\mathbf{R^c}$ and

R^c is as hereinbefore defined.

In other preferred embodiments **(E6)** the present invention relates to compounds of the preferred embodiments **(E3)** and/or **(E4)** and/or **(E5)**, wherein

R^{c1} is selected from among C_{1-4}alkyl, C_{3-5}cycloalkyl, C_{1-4}alkoxymethyl, (C_{1-4}alkyl)NH-CH_2- and (C_{1-4}alkyl)$_2$N-CH_2-.

In other preferred embodiments **(E7)** the present invention relates to compounds of the preferred embodiments **(E3)** and/or **(E4)** and/or **(E5)**, wherein

R^{c1} is selected from methyl and ethyl.

In another preferred embodiment **(E8)** the present invention relates to compounds of general formula **(1)**, wherein

R^3 is selected from -NHS(O)$_2$Me and -N(Me)S(O)$_2$Me.

In another preferred embodiment **(F1)** the present invention relates to compounds of general formula **(1)**, wherein

A is a group selected from phenyl and 5-10 membered heteroaryl and

R^1, R^2 and **m** are as hereinbefore defined.

In another preferred embodiment **(F2)** the present invention relates to compounds of general formula **(1)**, wherein

A is phenyl or pyridyl and

R^1, R^2 and **m** are as hereinbefore defined.

In another preferred embodiment **(F3)** the present invention relates to compounds of general formula **(1)**, wherein

A is phenyl and

R^1, R^2 and **m** are as hereinbefore defined.

In another preferred embodiment **(F4)** the present invention relates to compounds of general formula **(1)**, wherein

A is a phenyl;

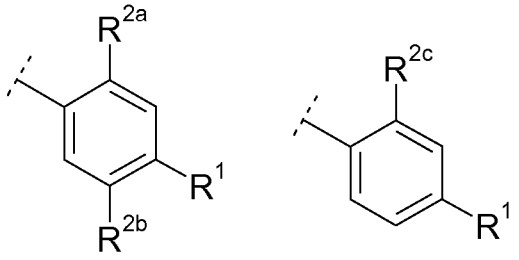
m has the value 1 or 2;

each $\mathbf{R^2}$ is independently selected from among halogen, $C_{1\text{-}6}$alkyl and $C_{1\text{-}6}$alkoxy and

$\mathbf{R^1}$ is as hereinbefore defined.

In another preferred embodiment **(F5)** the present invention relates to compounds of general formula **(1)**, wherein

A together with $\mathbf{R^1}$ and the **m** substituents $\mathbf{R^2}$ has the partial structure



(i) or **(ii)** ;

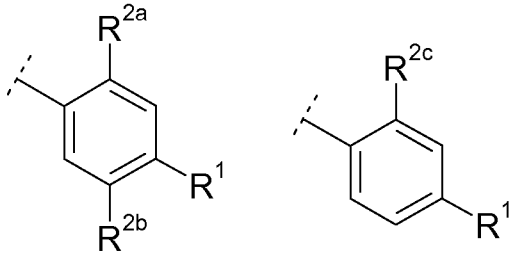
$\mathbf{R^{2a}}$ and $\mathbf{R^{2c}}$ each independently denote $C_{1\text{-}6}$alkoxy;

$\mathbf{R^{2b}}$ is selected from among halogen and $C_{1\text{-}6}$alkyl and

$\mathbf{R^1}$ is as hereinbefore defined.

In another preferred embodiment **(F6)** the present invention relates to compounds of general formula **(1)**, wherein

A together with $\mathbf{R^1}$ and the **m** substituents $\mathbf{R^2}$ has the partial structure



(i) or **(ii)** ;

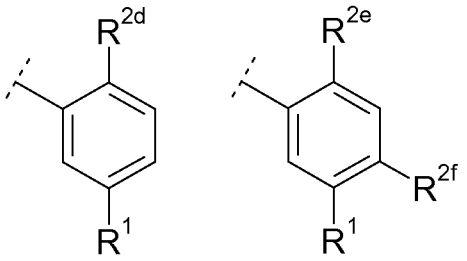
$\mathbf{R^{2a}}$ and $\mathbf{R^{2c}}$ each independently denote methoxy;

$\mathbf{R^{2b}}$ is selected from among fluorine, chlorine, methyl and ethyl and

$\mathbf{R^1}$ is as hereinbefore defined.

In another preferred embodiment **(F7)** the present invention relates to compounds of general formula **(1)**, wherein

A together with R^1 and the **m** substituents R^2 has the partial structure



(iii) or **(iv)** ;

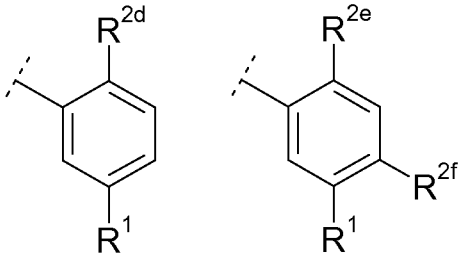
R^{2d} and R^{2e} each independently denote C_{1-6}alkoxy;

R^{2f} is selected from among halogen and C_{1-6}alkyl and

R^1 are as hereinbefore defined.

In another preferred embodiment **(F8)** the present invention relates to compounds of general formula **(1)**, wherein

A together with R^1 and the **m** substituents R^2 has the partial structure



(iii) or **(iv)** ;

R^{2d} and R^{2e} each independently denote methoxy;

R^{2f} is selected from among fluorine and methyl and

R^1 is as hereinbefore defined.

In other preferred embodiments **(F9)** the present invention relates to compounds of the preferred embodiments **(F1)** to **(F8)**, wherein

$\mathbf{R^1}$ is selected from among $\mathbf{R^{a2}}$, $\mathbf{R^{b2}}$ and $\mathbf{R^{a2}}$ substituted by one or more, identical or different $\mathbf{R^{b2}}$ and/or $\mathbf{R^{c2}}$;

each $\mathbf{R^{a2}}$ is independently selected from among C_{1-6}alkyl and 3-7 membered heterocycloalkyl;

each $\mathbf{R^{b2}}$ is a suitable substituent and is independently selected from among O=, $-OR^{c2}$, $-NR^{c2}R^{c2}$, $-C(O)R^{c2}$, $-C(O)OR^{c2}$, $-C(O)NR^{c2}R^{c2}$, $-C(O)N(R^{g2})OR^{c2}$, $-N(R^{g2})C(O)R^{c2}$, $-N(R^{g2})C(O)OR^{c2}$ and $-N(R^{g2})C(O)NR^{c2}R^{c2}$,

each $\mathbf{R^{c2}}$ independently denotes hydrogen or a group optionally substituted by one or more, identical or different $\mathbf{R^{d2}}$ and/or $\mathbf{R^{e2}}$, selected from among C_{1-6}alkyl, C_{3-6}cycloalkyl and 3-7 membered heterocycloalkyl;

each $\mathbf{R^{d2}}$ denotes a suitable substituent and is independently selected from among $-OR^{e2}$, $-NR^{e2}R^{e2}$ and $-C(O)N(R^{g2})OR^{e2}$,$-C(O)NR^{e2}R^{e2}$;

each $\mathbf{R^{e2}}$ independently denotes hydrogen or a group optionally substituted by one or more, identical or different $\mathbf{R^{f2}}$ and/or $\mathbf{R^{g2}}$, selected from among C_{1-6}alkyl, C_{3-6}cycloalkyl and 3-7 membered heterocycloalkyl;

each $\mathbf{R^{f2}}$ independently denotes $-OR^{g2}$ and

each $\mathbf{R^{g2}}$ is independently selected from among hydrogen, C_{1-6}alkyl and C_{4-9}cycloalkylalkyl.

In other preferred embodiments **(F10)** the present invention relates to compounds of the preferred embodiments **(F9)**, wherein

$\mathbf{R^1}$ denotes $-C(O)NHR^{c2}$ or $-C(O)N(Me)R^{c2}$ and

$\mathbf{R^{c2}}$ is as hereinbefore defined.

In other preferred embodiments **(F11)** the present invention relates to compounds of the preferred embodiments **(F9)**, wherein

$\mathbf{R^1}$ denotes $-NHC(O)R^{c2}$ or $-N(Me)C(O)R^{c2}$ and

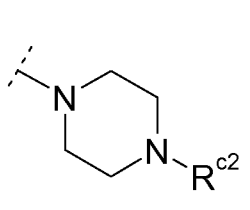
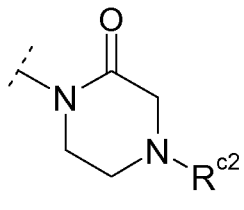
$\mathbf{R^{c2}}$ is as hereinbefore defined.

In other preferred embodiments **(F12)** the present invention relates to compounds of the preferred embodiments **(F9)** to **(F11)**, wherein

a heterocycloalkyl R^{a2} and/or R^{c2} is a heterocycloalkyl selected from among piperidinyl, piperazinyl, pyrrolidinyl, tetrahydropyranyl and morpholinyl.

In other preferred embodiments **(F13)** the present invention relates to compounds of the preferred embodiments **(F9)**, wherein

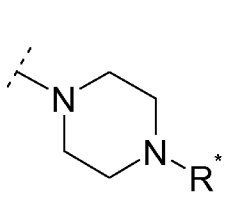
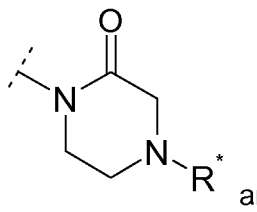
R^1 denotes

 or  and

R^{c2} is as hereinbefore defined.

In other preferred embodiments **(F14)** the present invention relates to compounds of the preferred embodiments **(F9)**, wherein

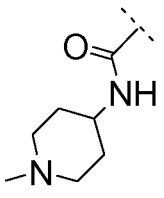
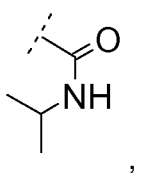
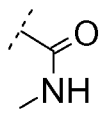
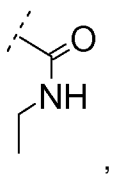
R^1 denotes

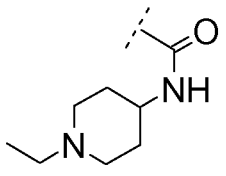
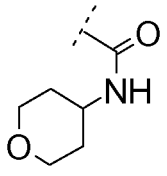
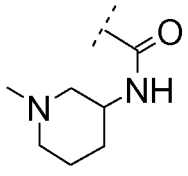
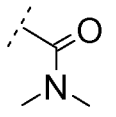
 or  and

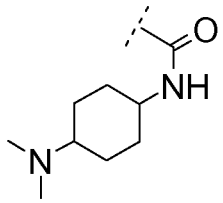
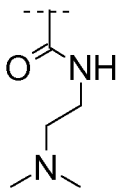
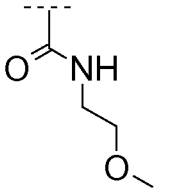
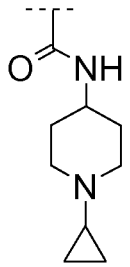
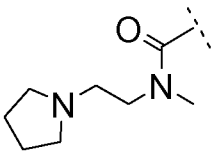
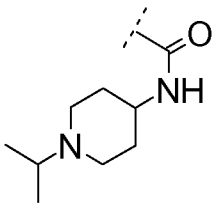
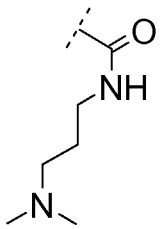
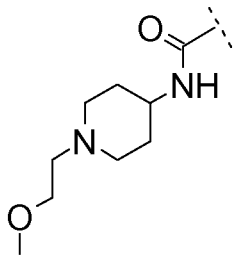
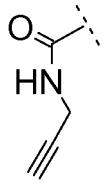
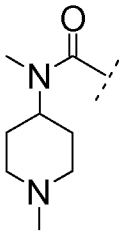
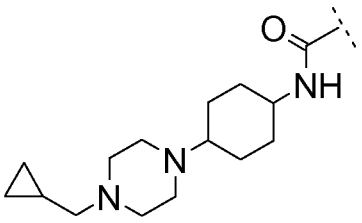
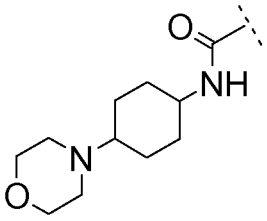
R^* denotes $C_{1\text{-}6}$alkyl.

In other preferred embodiments **(F15)** the present invention relates to compounds of the preferred embodiments **(F9)**, wherein

R^1 is selected from among

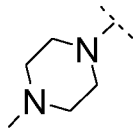
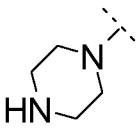
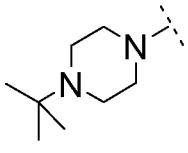
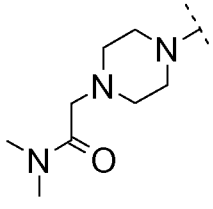
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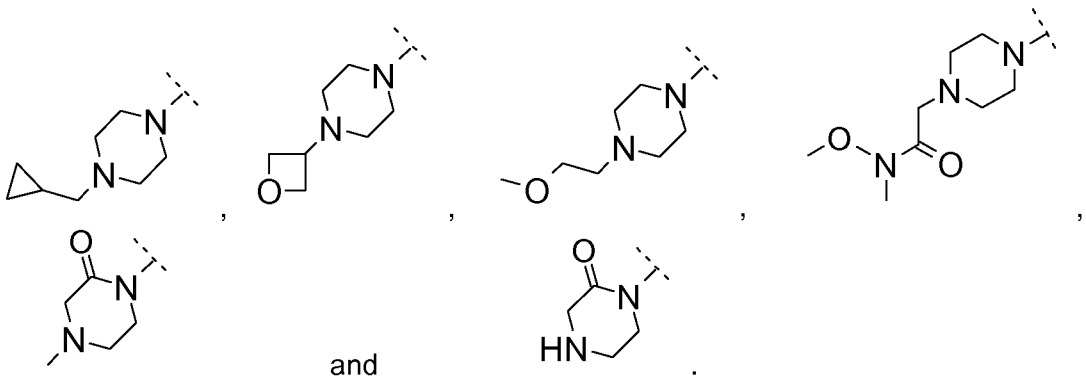
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In other preferred embodiments **(F16)** the present invention relates to compounds of the preferred embodiments **(F9)**, wherein

R^1 is selected from among

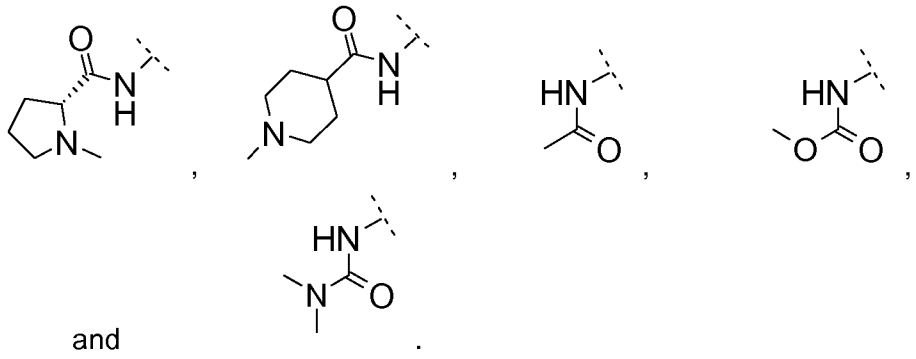

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In other preferred embodiments **(F17)** the present invention relates to compounds of the preferred embodiments **(F9)**, wherein

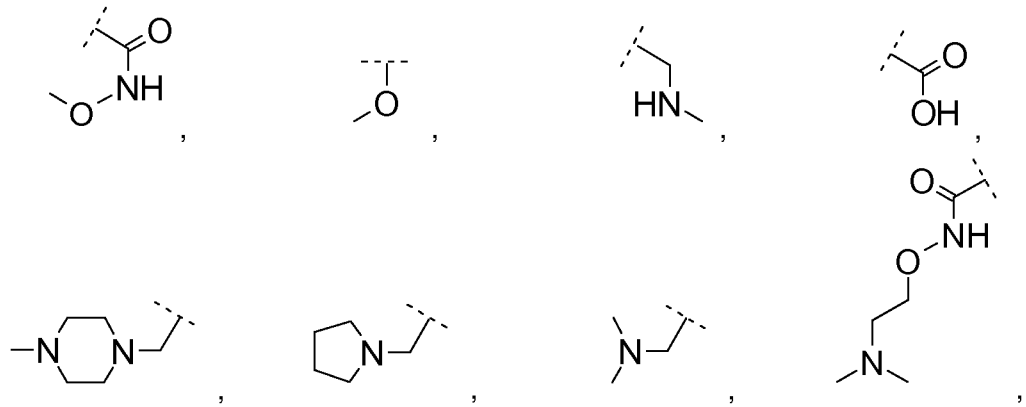
R^1 is selected from among

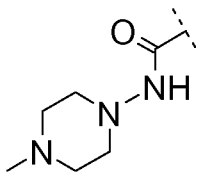
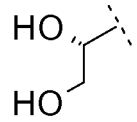
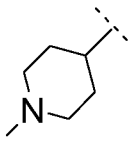
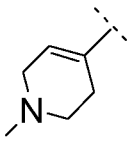
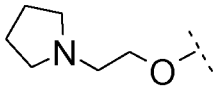


and .

In other preferred embodiments **(F18)** the present invention relates to compounds of the preferred embodiments **(F9)**, wherein

R^1 is selected from among

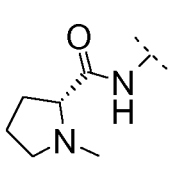
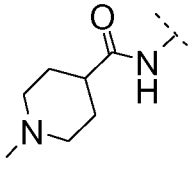
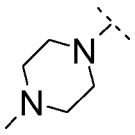
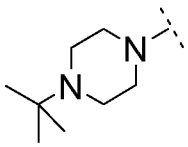


and .

In other preferred embodiments **(F19)** the present invention relates to compounds of the preferred embodiments **(F9)**, wherein

$\mathbf{R^1}$ is selected from among




and

.

In other preferred embodiments the present invention relates to compounds of all the foregoing embodiments, wherein

each $\mathbf{R^a}$ is independently selected from among $C_{1\text{-}6}$alkyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}16}$cycloalkylalkyl, $C_{6\text{-}10}$aryl, $C_{7\text{-}16}$arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each $\mathbf{R^b}$ denotes a suitable group and is independently selected from among =O, $-OR^c$, $C_{1\text{-}3}$haloalkyloxy, $-OCF_3$, $-NR^cR^c$, $-ONR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, halogen, $-CF_3$, -CN, $-NO_2$, $-S(O)_2R^c$, $-S(O)_2NR^cR^c$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)NR^cR^c$, $-C(O)N(R^g)NR^cR^c$, $-C(O)N(R^g)OR^c$, $-OC(O)R^c$, $-OC(O)NR^cR^c$, $-N(R^g)C(O)R^c$, $-N(OR^g)C(O)R^c$, $-N(R^g)S(O)_2R^c$, $-N(R^g)C(O)OR^c$ and $-N(R^g)C(O)NR^cR^c$;

each $\mathbf{R^c}$ independently denotes hydrogen or a group optionally substituted by one or more, identical or different $\mathbf{R^d}$ and/or $\mathbf{R^e}$, selected from among $C_{1\text{-}6}$alkyl, $C_{3\text{-}10}$cycloalkyl, $C_{4\text{-}11}$cycloalkylalkyl, $C_{6\text{-}10}$aryl, $C_{7\text{-}16}$arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^d** denotes a suitable group and is independently selected from among =O, -OR^e, C_{1-3}haloalkyloxy, -OCF$_3$, -NR^{e}R^e, -ONR^{e}R^e, -N(R^g)NR^{e}R^e, halogen, -CF$_3$, -CN, -NO$_2$, -S(O)$_2$R^e, -S(O)$_2$NR^{e}R^e, -C(O)R^e, -C(O)OR^e, -C(O)NR^{e}R^e, -C(O)N(R^g)NR^{e}R^e, -C(O)N(R^g)OR^e, -OC(O)R^e, -OC(O)NR^{e}R^e, -N(R^g)C(O)R^e, -N(OR^g)C(O)R^e, -N(R^g)S(O)$_2$R^e, -N(R^g)C(O)OR^e and -N(R^g)C(O)NR^{e}R^e;

each **R^e** independently denotes hydrogen or a group optionally substituted by one or more, identical or different **R^f** and/or **R^g**, selected from among C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{4-11}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^f** denotes a suitable group and is independently selected from among halogen, -OR^g and -CF$_3$ and

each **R^g** independently denotes hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{4-11}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkyl, 5-12 membered heteroaryl or 6-18 membered heteroarylalkyl.

All the above-mentioned preferred embodiments in terms of different molecular parts of the compounds according to the invention **(1)** may be combined with one another in any desired manner, thus producing preferred compounds **(1)** according to the invention or generic partial amounts of preferred compounds according to the invention **(1)**. Each individual embodiment or partial amount defined by this combination is expressly also included and is an object of the invention.

Particularly preferred compounds of general formula **(1)** are:

I-3 *N*-(2-dimethylamino-ethyl)-4-[4-((1*R*,2*R*)-1-methanesulphonylamino-indan-2-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-3-methoxy-benzamide;

I-5 4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-39 *N*-((1*R*,2*R*)-2-{2-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-5-trifluoromethyl-pyrimidin-4-ylamino}-indan-1-yl)-*N*-methyl-methanesulphonamide;

I-40 2-[4-(4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-

trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-phenyl)-piperazin-1-yl]-*N*,*N*-dimethyl-acetamide;

I-46 2-fluoro-4-{4-[(1*R* ,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-60 2-chloro-4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-61 1-methyl-pyrrolidine-3-carboxylic acid (3-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-4-methoxy-phenyl)-amide;

I-62 1-methyl-piperidine-4-carboxylic acid (3-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-4-methoxy-phenyl)-amide;

I-63 *N*-(2-dimethylamino-ethyl)-3-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-4-methoxy-benzamide;

I-66 *N*-((1*R*,2*R*)-2-{2-[4-(4-*tert*-butyl-piperazin-1-yl)-2-methoxy-phenylamino]-5-trifluoromethyl-pyrimidin-4-ylamino}-indan-1-yl)-*N*-methyl-methanesulphonamide;

I-67 *N*-((1*R*,2*R*)-2-{2-[5-ethyl-2-methoxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-5-trifluoromethyl-pyrimidin-4-ylamino}-indan-1-yl)-*N*-methyl-methanesulphonamide;

I-70 *N*-{(1*R*,2*R*)-2-[2-(2-methoxy-4-piperazin-1-yl-phenylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-indan-1-yl}-*N*-methyl-methanesulphonamide;

I-74 *N*-{(1*R*,2*R*)-2-[2-(2-methoxy-5-methyl-4-piperazin-1-yl-phenylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-indan-1-yl}-*N*-methyl-methanesulphonamide;

I-75 5-{5-chloro-4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-pyrimidin-2-ylamino}-2-fluoro-4-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-76 *N*-{(1*R*,2*R*)-2-[2-(5-chloro-2-methoxy-4-piperazin-1-yl-phenylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-indan-1-yl}-*N*-methyl-methanesulphonamide;

I-78 *N*-((1*R*,2*R*)-2-{2-[4-(4-*tert*-butyl-piperazin-1-yl)-2-methoxy-5-methyl-phenylamino]-5-trifluoromethyl-pyrimidin-4-ylamino}-indan-1-yl)-*N*-methyl-methanesulphonamide;

I-80 2-fluoro-5-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-4-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-98 4-{5-bromo-4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-pyrimidin-2-ylamino}-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-73 1-methyl-piperidine-4-carboxylic acid (4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-phenyl)-amide and

I-71 *N*-{(1*R*,2*R*)-2-[2-(2-methoxy-4-methylaminomethyl-phenylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-indan-1-yl}-*N*-methyl-methanesulphonamide.

The present invention further relates to hydrates, solvates, polymorphs, metabolites, derivatives and prodrugs of compounds of general formula **(1)**.

In another aspect the invention relates to compounds of general formula **(1)** – or the pharmaceutically acceptable salts thereof – as medicaments.

In another aspect the invention relates to compounds of general formula **(1)** – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of cancer, infections, inflammations and autoimmune diseases.

In another aspect the invention relates to compounds of general formula **(1)** – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of cancer.

In another aspect the invention relates to compounds of general formula **(1)** – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of prostate cancer, ovarian cancer, pancreatic cancer and bronchial cancer.

In another aspect the invention relates to a process for the treatment and/or prevention of cancer comprising administering a therapeutically effective amount of a compound of general formula **(1)** – or one of the pharmaceutically acceptable salts thereof – to a person.

In another aspect the invention relates to a pharmaceutical preparation containing as active substance one or more compounds of general formula **(1)** – or the pharmaceutically acceptable salts thereof – optionally in combination with conventional excipients and/or carriers.

In another aspect the invention relates to a pharmaceutical preparation comprising a compound of general formula **(1)** – or one of the pharmaceutically acceptable salts thereof – and at least one other cytostatic or cytotoxic active substance different from formula **(1).**

Definitions

As used herein, the following definitions apply, unless stated otherwise:

Alkyl is made up of the sub-groups saturated hydrocarbon chains and unsaturated hydrocarbon chains, while the latter may be further subdivided into hydrocarbon chains with a double bond (alkenyl) and hydrocarbon chains with a triple bond (alkynyl). Alkenyl contains at least one double bond, alkynyl contains at least one triple bond. If a hydrocarbon chain were to carry both at least one double bond and also at least one triple bond, by definition it would belong to the alkynyl sub-group. All the sub-groups mentioned above may further be divided into straight-chain (unbranched) and branched. If an alkyl is substituted, the substitution may be mono- or polysubstitution in each case, at all the hydrogen-carrying carbon atoms, independently of one another.
Examples of representatives of individual sub-groups are listed below.

Straight-chain (unbranched) or branched saturated hydrocarbon chains:

methyl; ethyl; *n*-propyl; isopropyl (1-methylethyl); *n*-butyl; 1-methylpropyl; isobutyl (2-methylpropyl); *sec.*-butyl (1-methylpropyl); *tert.*-butyl (1,1-dimethylethyl); *n*-pentyl; 1-methylbutyl; 1-ethylpropyl; isopentyl (3-methylbutyl); neopentyl (2,2-dimethyl-propyl); *n*-hexyl; 2,3-dimethylbutyl; 2,2-dimethylbutyl; 3,3-dimethylbutyl; 2-methyl-pentyl; 3-methylpentyl; *n*-heptyl; 2-methylhexyl; 3-methylhexyl; 2,2-dimethylpentyl; 2,3-dimethylpentyl; 2,4-dimethylpentyl; 3,3-dimethylpentyl; 2,2,3-trimethylbutyl; 3-ethylpentyl; *n*-octyl; *n*-nonyl; *n*-decyl etc.

Straight-chain (unbranched) or branched alkenyl:

vinyl (ethenyl); prop-1-enyl; allyl (prop-2-enyl); isopropenyl; but-1-enyl; but-2-enyl; but-3-enyl; 2-methyl-prop-2-enyl; 2-methyl-prop-1-enyl; 1-methyl-prop-2-enyl; 1-methyl-prop-1-enyl; 1-methylidenepropyl; pent-1-enyl; pent-2-enyl; pent-3-enyl; pent-4-enyl; 3-methyl-but-3-enyl; 3-methyl-but-2-enyl; 3-methyl-but-1-enyl; hex-1-enyl; hex-2-enyl; hex-3-enyl; hex-4-enyl; hex-5-enyl; 2,3-dimethyl-but-3-enyl; 2,3-dimethyl-but-2-enyl; 2-methylidene-3-

methylbutyl; 2,3-dimethyl-but-1-enyl; hexa-1,3-dienyl; hexa-1,4-dienyl; penta-1,4-dienyl; penta-1,3-dienyl; buta-1,3-dienyl; 2,3-dimethylbuta-1,3-diene etc.

Straight-chain (unbranched) or branched alkynyl:

ethynyl; prop-1-ynyl; prop-2-ynyl; but-1-ynyl; but-2-ynyl; but-3-ynyl; 1-methyl-prop-2-ynyl etc.

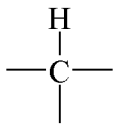
By the terms propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl etc. without any further definition are meant saturated hydrocarbon groups with the corresponding number of carbon atoms, all the isomeric forms being included.

By the terms propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl etc. without any further definition are meant unsaturated hydrocarbon groups with the corresponding number of carbon atoms and a double bond, all the isomeric forms, i.e. (*Z*)/(*E*) isomers, being included where applicable.

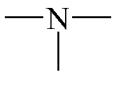
By the terms butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, nonadienyl, decadienyl etc. without any further definition are meant unsaturated hydrocarbon groups with the corresponding number of carbon atoms and two double bonds, all the isomeric forms, i.e. (*Z*)/(*E*) isomers, being included where applicable.

By the terms propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl etc. without any further definition are meant unsaturated hydrocarbon groups with the corresponding number of carbon atoms and a triple bond, all the isomeric forms being included.

By the term heteroalkyl are meant groups which can be derived from the alkyl as defined above in its broadest sense if, in the hydrocarbon chains, one or more of the groups $-CH_3$ are replaced independently of one another by the groups –OH, –SH or $-NH_2$, one or more of the groups $-CH_2-$ are replaced independently of one another by the groups –O–, –S– or –NH– , one or more of the groups



are replaced by the group



,

one or more of the groups =CH– are replaced by the group =N–, one or more of the groups $=CH_2$ are replaced by the group =NH or one or more of the groups ≡CH are replaced by the group ≡N, while overall there may only be a maximum of three heteroatoms in a heteroalkyl, there must be at least one carbon atom between two oxygen atoms and between two sulphur atoms or between one oxygen and one sulphur atom and the group as a whole must be chemically stable.

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

Typical examples are listed below:

dimethylaminomethyl; dimethylaminoethyl (1- dimethylaminoethyl; 2-dimethyl-aminoethyl); dimethylaminopropyl (1-dimethylaminopropyl, 2-dimethylaminopropyl, 3-dimethylaminopropyl); diethylaminomethyl; diethylaminoethyl (1-diethylaminoethyl, 2-diethylaminoethyl); diethylaminopropyl (1-diethylaminopropyl, 2- diethylamino-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.

Halogen denotes fluorine, chlorine, bromine and/or iodine atoms.

Haloalkyl is derived from alkyl as hereinbefore defined in its broadest sense, when one or more hydrogen atoms of the hydrocarbon chain are replaced independently of one another by halogen atoms, which may be identical or different. It is immediately apparent from the indirect definition/derivation from alkyl that haloalkyl is made up of the sub-groups saturated halohydrocarbon chains, haloalkenyl and haloalkynyl, and further

subdivision may be made into straight-chain (unbranched) and branched. If a haloalkyl is substituted, the substitution may be mono- or polysubstitution in each case, at all the hydrogen-carrying carbon atoms, independently of one another.
Typical examples include $-CF_3$; $-CHF_2$; $-CH_2F$; $-CF_2CF_3$; $-CHFCF_3$; $-CH_2CF_3$; $-CF_2CH_3$; $-CHFCH_3$; $-CF_2CF_2CF_3$; $-CF_2CH_2CH_3$; $-CF=CF_2$; $-CCl=CH_2$; $-CBr=CH_2$; $-Cl=CH_2$; $-C\equiv C-CF_3$; $-CHFCH_2CH_3$; and $-CHFCH_2CF_3$.

Cycloalkyl is made up of the sub-groups monocyclic hydrocarbon rings, bicyclic hydrocarbon rings and spirohydrocarbon rings, while each sub-group may be further subdivided into saturated and unsaturated (cycloalkenyl). The term unsaturated means that in the ring system in question there is at least one double bond, but no aromatic system is formed. In bicyclic hydrocarbon rings two rings are linked such that they have at least two carbon atoms in common. In spirohydrocarbon rings one carbon atom (spiroatom) is shared by two rings. If a cycloalkyl is substituted, the substitution may be mono- or polysubstitution in each case, at all the hydrogen-carrying carbon atoms, independently of one another. Cycloalkyl itself may be linked to the molecule as substituent via any suitable position of the ring system.
Typical examples of individual sub-groups are listed below.

<u>monocyclic saturated hydrocarbon rings:</u>

cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; cycloheptyl etc.

<u>monocyclic unsaturated hydrocarbon rings:</u>

cycloprop-1-enyl; cycloprop-2-enyl; cyclobut-1-enyl; cyclobut-2-enyl; cyclopent-1-enyl; cyclopent-2-enyl; cyclopent-3-enyl; cyclohex-1-enyl; cyclohex-2-enyl; cyclohex-3-enyl; cyclohept-1-enyl; cyclohept-2-enyl; cyclohept-3-enyl; cyclohept-4-enyl; cyclobuta-1,3-dienyl; cyclopenta-1,4-dienyl; cyclopenta-1,3-dienyl; cyclopenta-2,4-dienyl; cyclohexa-1,3-dienyl; cyclohexa-1,5-dienyl; cyclohexa-2,4-dienyl; cyclohexa-1,4-dienyl; cyclohexa-2,5-dienyl etc.

<u>saturated and unsaturated bicyclic hydrocarbon rings:</u>

bicyclo[2.2.0]hexyl; bicyclo[3.2.0]heptyl; bicyclo[3.2.1]octyl; bicyclo[2.2.2]octyl; bicyclo[4.3.0]nonyl (octahydroindenyl); bicyclo[4.4.0]decyl (decahydronaphthalene); bicyclo[2,2,1]heptyl (norbornyl); (bicyclo[2.2.1]hepta-2,5-dienyl (norborna-2,5-dienyl);

bicyclo[2,2,1]hept-2-enyl (norbornenyl); bicyclo[4.1.0]heptyl (norcaranyl); bicyclo-[3.1.1]heptyl (pinanyl) etc.

saturated and unsaturated spirohydrocarbon rings:

spiro[2.5]octyl, spiro[3.3]heptyl, spiro[4.5]dec-2-ene etc.

Cycloalkylalkyl denotes the combination of the above-defined groups alkyl and cycloalkyl, in each case in their broadest sense. The alkyl group as substituent is directly linked to the molecule and is in turn substituted by a cycloalkyl group. The alkyl and cycloalkyl may be linked in both groups via any carbon atoms suitable for this purpose. The respective sub-groups of alkyl and cycloalkyl are also included in the combination of the two groups.

Aryl denotes mono-, bi- or tricyclic carbon rings with at least one aromatic ring. If an aryl is substituted, the substitution may be mono- or polysubstitution in each case, at all the hydrogen-carrying carbon atoms, independently of one another. Aryl itself may be linked to the molecule as substituent via any suitable position of the ring system.
Typical examples include phenyl, naphthyl, indanyl (2,3-dihydroindenyl), 1,2,3,4-tetrahydronaphthyl and fluorenyl.

Arylalkyl denotes the combination of the groups alkyl and aryl as hereinbefore defined, in each case in their broadest sense. The alkyl group as substituent is directly linked to the molecule and is in turn substituted by an aryl group. The alkyl and aryl may be linked in both groups via any carbon atoms suitable for this purpose. The respective sub-groups of alkyl and aryl are also included in the combination of the two groups.

Typical examples include benzyl; 1-phenylethyl; 2-phenylethyl; phenylvinyl; phenylallyl etc.

Heteroaryl denotes monocyclic aromatic rings or polycyclic rings with at least one aromatic ring, which, compared with corresponding aryl or cycloalkyl, contain instead of one or more carbon atoms one or more identical or different heteroatoms, selected independently of one another from among nitrogen, sulphur and oxygen, while the resulting group must be chemically stable. If a heteroaryl is substituted, the substitution may be mono- or polysubstitution in each case, at all the hydrogen-carrying carbon and/or nitrogen atoms, independently of one another. Heteroaryl itself as substituent may be

linked to the molecule via any suitable position of the ring system, both carbon and nitrogen.
Typical examples are listed below.

monocyclic heteroaryls:

furyl; thienyl; pyrrolyl; oxazolyl; thiazolyl; isoxazolyl; isothiazolyl; pyrazolyl; imidazolyl; triazolyl; tetrazolyl; oxadiazolyl; thiadiazolyl; pyridyl; pyrimidyl; pyridazinyl; pyrazinyl; triazinyl; pyridyl-*N*-oxide; pyrrolyl-*N*-oxide; pyrimidinyl-*N*-oxide; pyridazinyl-*N*-oxide; pyrazinyl-*N*-oxide; imidazolyl-*N*-oxide; isoxazolyl-*N*-oxide; oxazolyl-*N*-oxide; thiazolyl-*N*-oxide; oxadiazolyl-*N*-oxide; thiadiazolyl-*N*-oxide; triazolyl-*N*-oxide; tetrazolyl-*N*-oxide etc.

polycyclic heteroaryls:

indolyl; isoindolyl; benzofuryl; benzothienyl; benzoxazolyl; benzothiazolyl; benzisoxazolyl; benzisothiazolyl; benzimidazolyl; indazolyl; isoquinolinyl; quinolinyl; quinoxalinyl; cinnolinyl; phthalazinyl; quinazolinyl; benzotriazinyl; indolizinyl; oxazolopyridyl; imidazopyridyl; naphthyridinyl; indolinyl; isochromanyl; chromanyl; tetrahydroisoquinolinyl; isoindolinyl; isobenzotetrahydrofuryl; isobenzotetrahydrothienyl; isobenzothienyl; benzoxazolyl; pyridopyridyl; benzotetrahydrofuryl; benzotetrahydro-thienyl; purinyl; benzodioxolyl; phenoxazinyl; phenothiazinyl; pteridinyl; benzothiazolyl; imidazopyridyl; imidazothiazolyl; dihydrobenzisoxazinyl; benzisoxazinyl; benzoxazinyl; dihydrobenzisothiazinyl; benzopyranyl; benzothiopyranyl; cumarinyl; isocumarinyl; chromonyl; chromanonyl; tetrahydroquinolinyl; dihydroquinolinyl; dihydroquinolinonyl; dihydroisoquinolinonyl; dihydrocumarinyl; dihydroisocumarinyl; isoindolinonyl; benzodioxanyl; benzoxazolinonyl; quinolinyl-*N*-oxide; indolyl-*N*-oxide; indolinyl-*N*-oxide; isoquinolyl-*N*-oxide; quinazolinyl-*N*-oxide; quinoxalinyl-*N*-oxide; phthalazinyl-*N*-oxide; indolizinyl-*N*-oxide; indazolyl-*N*-oxide; benzothiazolyl-*N*-oxide; benzimidazolyl-*N*-oxide; benzo-thiopyranyl-*S*-oxide and benzothiopyranyl-*S,S*-dioxide etc.

Heteroarylalkyl denotes the combination of the alkyl and heteroaryl groups defined hereinbefore, in each case in their broadest sense. The alkyl group as substituent is directly linked to the molecule and is in turn substituted by a heteroaryl group. The linking of the alkyl and heteroaryl may be achieved on the alkyl side via any carbon atoms suitable for this purpose and on the heteroaryl side by any carbon or nitrogen atoms suitable for this purpose. The respective sub-groups of alkyl and heteroaryl are also included in the combination of the two groups.

By the term heterocycloalkyl are meant groups which are derived from the cycloalkyl as hereinbefore defined if in the hydrocarbon rings one or more of the groups $-CH_2-$ are replaced independently of one another by the groups –O–, –S– or –NH– or one or more of the groups =CH– are replaced by the group =N–, while not more than five heteroatoms may be present in total, there must be at least one carbon atom between two oxygen atoms and between two sulphur atoms or between one oxygen and one sulphur atom and the group as a whole must be chemically stable. Heteroatoms may simultaneously be present in all the possible oxidation stages (sulphur → sulphoxide –SO–, sulphone $-SO_2-$; nitrogen → N-oxide). It is immediately apparent from the indirect definition/derivation from cycloalkyl that heterocycloalkyl is made up of the sub-groups monocyclic hetero-rings, bicyclic hetero-rings and spirohetero-rings, while each sub-group can also be further subdivided into saturated and unsaturated (heterocycloalkenyl). The term unsaturated means that in the ring system in question there is at least one double bond, but no aromatic system is formed. In bicyclic hetero-rings two rings are linked such that they have at least two atoms in common. In spirohetero-rings one carbon atom (spiroatom) is shared by two rings. If a heterocycloalkyl is substituted, the substitution may be mono- or polysubstitution in each case, at all the hydrogen-carrying carbon and/or nitrogen atoms, independently of one another. Heterocycloalkyl itself as substituent may be linked to the molecule via any suitable position of the ring system.

Typical examples of individual sub-groups are listed below.

<u>monocyclic heterorings (saturated and unsaturated):</u>

tetrahydrofuryl; pyrrolidinyl; pyrrolinyl; imidazolidinyl; thiazolidinyl; imidazolinyl; pyrazolidinyl; pyrazolinyl; piperidinyl; piperazinyl; oxiranyl; aziridinyl; azetidinyl; 1,4-dioxanyl; azepanyl; diazepanyl; morpholinyl; thiomorpholinyl; homomorpholinyl; homopiperidinyl; homopiperazinyl; homothiomorpholinyl; thiomorpholinyl-*S*-oxide; thiomorpholinyl-*S,S*-dioxide; 1,3-dioxolanyl; tetrahydropyranyl; tetrahydrothiopyranyl; [1,4]-oxazepanyl; tetrahydrothienyl; homothiomorpholinyl-*S,S*-dioxide; oxazolidinonyl; dihydropyrazolyl; dihydropyrrolyl; dihydropyrazinyl; dihydropyridyl; dihydro-pyrimidinyl; dihydrofuryl; dihydropyranyl; tetrahydrothienyl-*S*-oxide; tetrahydrothienyl-*S,S*-dioxide; homothiomorpholinyl-*S*-oxide; 2,3-dihydroazet; 2*H*-pyrrolyl; 4*H*-pyranyl; 1,4-dihydropyridinyl etc.

bicyclic heterorings (saturated and unsaturated):

8-azabicyclo[3.2.1]octyl; 8-azabicyclo[5.1.0]octyl; 2-oxa-5-azabicyclo[2.2.1]heptyl; 8-oxa-3-aza-bicyclo[3.2.1]octyl; 3,8-diaza-bicyclo[3.2.1]octyl; 2,5-diaza-bicyclo-[2.2.1]heptyl; 1-aza-bicyclo[2.2.2]octyl; 3,8-diaza-bicyclo[3.2.1]octyl; 3,9-diaza-bicyclo[4.2.1]nonyl; 2,6-diaza-bicyclo[3.2.2]nonyl; hexahydro-furo[3,2-b]furyl; etc.

spiro-heterorings (saturated and unsaturated):

1,4-dioxa-spiro[4.5]decyl; 1-oxa-3,8-diaza-spiro[4.5]decyl; and 2,6-diaza-spiro[3.3]heptyl; 2,7-diaza-spiro[4.4]nonyl; 2,6-diaza-spiro[3.4]octyl; 3,9-diaza-spiro[5.5]undecyl; 2,8-diaza-spiro[4.5]decyl etc.

Heterocycloalkylalkyl denotes the combination of the alkyl and heterocycloalkyl groups defined hereinbefore, in each case in their broadest sense. The alkyl group as substituent is directly linked to the molecule and is in turn substituted by a heterocycloalkyl group. The linking of the alkyl and heterocycloalkyl may be achieved on the alkyl side via any carbon atoms suitable for this purpose and on the heterocycloalkyl side by any carbon or nitrogen atoms suitable for this purpose. The respective sub-groups of alkyl and heterocycloalkyl are also included in the combination of the two groups.

By the term "suitable substituent" is meant a substituent that on the one hand is fitting on account of its valency and on the other hand leads to a system with chemical stability.

By "prodrug" is meant an active substance in the form of its precursor metabolite. A distinction may be made between partly multi-part carrier-prodrug systems and biotransformation systems. The latter contain the active substance in a form that requires chemical or biological metabolisation. The skilled man will be familiar with prodrug systems of this kind (Sloan, Kenneth B.; Wasdo, Scott C. The role of prodrugs in penetration enhancement. Percutaneous Penetration Enhancers (2nd Edition) (2006).51-64; Lloyd, Andrew W. Prodrugs. Smith and Williams' Introduction to the Principles of Drug Design and Action (4th Edition) (2006), 211-232; Neervannan, Seshadri. Strategies to impact solubility and dissolution rate during drug lead optimization: salt selection and prodrug design approaches. American Pharmaceutical Review (2004), 7(5), 108.110-113). A suitable prodrug contains for example a substance of the general formulae which is linked via an enzymatically cleavable linker (e.g. carbamate, phosphate, N-glycoside or

a disulphide group to a dissolution-improving substance (e.g. tetraethyleneglycol, saccharides, amino acids). Carrier-prodrug systems contain the active substance as such, bound to a masking group which can be cleaved by the simplest possible controllable mechanism. The function of masking groups according to the invention in the compounds according to the invention is to neutralise the charge for improving cell uptake. If the compounds according to the invention are used with a masking group, these may also additionally influence other pharmacological parameters, such as for example oral bioavailability, tissue distribution, pharmacokinetics and stability against non-specific phosphatases. The delayed release of the active substance may also involve a sustained-release effect. In addition, modified metabolisation may occur, thus resulting in a higher efficiency of the active substance or organic specificity. In the case of a prodrug formulation, the masking group or a linker that binds the masking group to the active substance is selected such that the prodrug is sufficiently hydrophilic to be dissolved in the blood serum, has sufficient chemical and enzymatic stability to reach the activity site and is also sufficiently hydrophilic to ensure that it is suitable for diffusion-controlled membrane transport. Furthermore, it should allow chemically or enzymatically induced release of the active substance within a reasonable period and, it goes without saying, the auxiliary components released should be non-toxic. Within the scope of the invention, however, the compound without a mask or linker, and a mask, may be regarded as a prodrug which first of all has to be prepared in the cell from the ingested compound by enzymatic and biochemical processes.

List of abbreviations

Ac	acetyl
Bu	butyl
c	concentration
cHex	cyclohexane
d	day(s)
TLC	thin layer chroma-tography
DCM	dichloromethane
DIPEA	*N*-ethyl-*N*,*N*-diiso-propylamine (Hünig base)
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulphoxide
EA	ethyl acetate
eq	equivalent(s)
ESI	electron spray ionization
Et	ethyl
EtOH	ethanol
h	hour(s)
Hex	hexyl
HPLC	high performance liquid chromatography
i	iso
IR	infra-red spectroscopy

LC	liquid chromatography
Me	methyl
MeOH	methanol
min	minute(s)
MPLC	medium pressure liquid chromatography
MS	mass spectrometry
NMP	N-methylpyrrolidone
NP	normal phase
Ph	phenyl
Pr	propyl
Rf (Rf)	retention factor
RP	reversed phase
RT	ambient temperature
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate
temp.	temperature
tert.	tertiary
THF	tetrahydrofuran
tRet.	retention time (HPLC)
UV	ultraviolet

Features and advantages of the present invention will become apparent from the following detailed Examples which illustrate the fundamentals of the invention by way of example, without restricting its scope:

Preparation of the compounds according to the invention

General

All the reactions are carried out – unless stated otherwise - in commercially obtainable apparatus using methods conventionally used in chemical laboratories.

Air- and/or moisture-sensitive starting materials are stored under protective gas and corresponding reactions and manipulations using them are carried out under protective gas (nitrogen or argon).

Microwave reactions are carried out in an Initiator made by Biotage or an Explorer made by CEM in sealed containers (preferably 2, 5 or 20 mL), preferably with stirring.

Chromatography

For the preparative medium pressure chromatography (MPLC, normal phase) silica gel is used which is made by Millipore (named: Granula Silica Si-60A 35-70 µm) or C-18 RP-silica gel (RP-phase) made by Macherey Nagel (named: Polygoprep 100-50 C18).
The thin layer chromatography is carried out on ready-made silica gel 60 TLC plates on glass (with fluorescence indicator F-254) made by Merck.
The preparative high pressure chromatography (HPLC) is carried out using columns made by Waters (named: XTerra Prep. MS C18, 5 µM, 30 x 100 mm or XTerra Prep. MS C18, 5 µm, 50 x 100 mm OBD or Symmetrie C18, 5 µm, 19 x 100 mm or Sunfire C18 OBD, 19 x 100 mm, 5 µm or Sunfire Prep C 10 µm OBD 50 x 150 mm or X-Bridge Prep C18 5 µm OBD 19 x 50 mm), Agilent (named: Zorbax SB-C8 5 µm PrepHT 21.2 x 50 mm) and Phenomenex (named: Gemini C18 5 µm AXIA 21.2 x 50 mm or Gemini C18 10 µm 50 x 150 mm), the analytical HPLC (reaction control) is carried out with columns made by Agilent (named: Zorbax SB-C8, 5 µm, 21.2 x 50 mm or Zorbax SB-C8 3.5 µm 2.1 x 50 mm) and Phenomenex (named: Gemini C18 3 µm 2 x 30 mm).

HPLC mass spectroscopy/UV spectrometry

The retention times/MS-ESI$^+$ for characterising the examples are obtained using an HPLC-MS apparatus (high performance liquid chromatography with mass detector) made by Agilent. Compounds that elute with the injection peak are given the retention time $t_{Ret.}$ = 0.00.

Method A:

Column:	Waters, Xterra MS C18, 2.5 µm, 2.1 x 30 mm, Part.No. 186000592	
Eluant:	A: H_2O with 0.1% HCOOH; B: acetonitrile (HPLC grade)	
Detection:	MS: Positive and negative mode	
Mass range:	120 – 900 m/z	
Fragmentor:	120	
Gain EMV:	1; Threshold: 150; Stepsize: 0.25; UV: 254 nm ; Bandwidth: 1	
Injection:	Inj. Vol. 5 µL	
Separation:	Flow 1.10 mL/min	
Column temp.:	40°C	
Gradient:	0.00 min:	5 % solvent B
	0.00 – 2.50 min:	5 % → 95 % solvent B
	2.50 – 2.80 min:	95 % solvent B
	2.81 – 3.10 min:	95 % → 5 % solvent B

Method B:

Column:	Waters, Xterra MS C18, 2.5 µm, 2.1 x 50 mm, Part.No. 186000594	
Eluant:	A: H_2O with 0.1 % HCOOH; B: acetonitrile with 0.1 % HCOOH	
Detection:	MS: Positive and negative mode	
Mass range:	100 – 1200 m/z	
Fragmentor:	70	
Gain EMV:	Threshold: 1 mAU; Stepsize: 2 nm; UV: 254 nm as well as 230 nm	
Injection:	Standard 1 µL	
Flow:	0.6 mL/min	
Column temp.:	35°C	
Gradient:	0.00 min:	5 % solvent B
	0.00 – 2.50 min:	5 % → 95 % solvent B
	2.50 – 4.00 min:	95 % solvent B
	4.00 – 4.50 min:	95 % → 5 % solvent B
	4.50 – 6.00 min:	95 % solvent A

Method C

Column:	Waters, X-Bridge C18, 3.5 µm, 2.1 x 50 mm,
Eluant:	A: H_2O with 10mM NH_3; B: acetonitrile with 10 nM NH_3
Detection:	MS: Positive and negative mode
Mass range:	100 – 800 m/z

Fragmentor:	70
Gain EMV:	Threshold: 1 mAU; Stepsize: 2 nm; UV: 220-320 nm
Injection:	Standard 1 µL
Flow:	0.8 mL/min
Column temp.:	25°C
Gradient:	0.00 min: 2 % solvent B
	0.00 – 4.00 min: 2 % → 98 % solvent B
	4.00 – 6.00 min: 98 % solvent B

Method D

Column:	Waters, X-Bridge C18, 3.5 µm, 2.1 x 50 mm,
Eluant:	A: H_2O with 0.1 % HCOOH; B: acetonitrile with 0.1 % HCOOH
Detection:	MS: Positive and negative mode
Mass range:	100 – 800 m/z
Fragmentor:	70
Gain EMV:	Threshold: 1 mAU; Stepsize: 2 nm; UV: 220-320 nm
Injection:	Standard 1 µL
Flow:	0.8 mL/min
Column temp.:	35°C
Gradient:	0.00 min: 2 % solvent B
	0.00 – 4.00 min: 2 % → 98 % solvent B
	4.00 – 6.00 min: 98 % solvent B

Method E

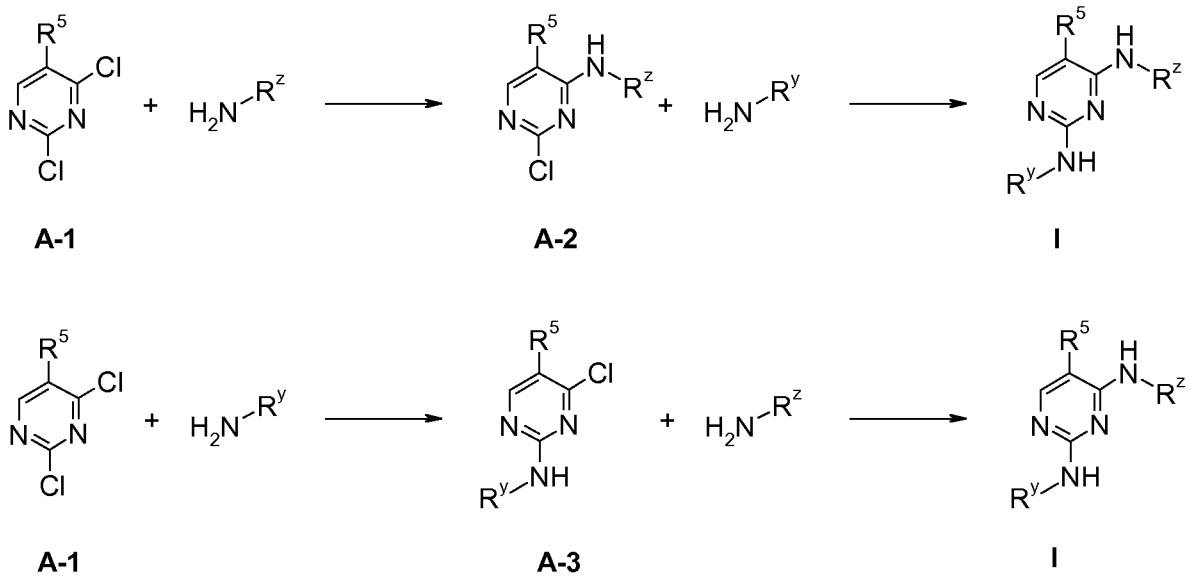
Column:	Phenomenex Gemini C18, 3.0 µm, 2.0 x 50 mm,
Eluant:	A: H_2O with 10 mM NH_3; B: acetonitrile with 10 nM NH_3
Detection:	MS: Positive and negative mode
Mass range:	100 – 800 m/z
Fragmentor:	70
Gain EMV:	Threshold: 1 mAU; Stepsize: 2 nm; UV: 220-320 nm
Injection:	Standard 1 µL
Flow:	1.0 mL/min
Column temp.:	35°C
Gradient:	0.00 min: 2 % solvent B
	0.00 – 3.50 min: 2 % → 98 % solvent B
	3.50 – 6.00 min: 98 % solvent B

Method F

Column:	Phenomenex Gemini C18, 3.0 µm, 2.0 x 50 mm,	
Eluant:	A: H_2O with 0.1 % HCOOH; B: acetonitrile with 0.1 % HCOOH	
Detection:	MS: Positive and negative mode	
Mass range:	100 – 800 m/z	
Fragmentor:	70	
Gain EMV:	Threshold: 1 mAU; Stepsize: 2 nm; UV: 220-320 nm	
Injection:	Standard 1 µL	
Flow:	1.0 mL/min	
Column temp.:	35°C	
Gradient:	0.00 min:	2 % solvent B
	0.00 – 3.50 min:	2 % → 98 % solvent B
	3.50 – 6.00 min:	95 % solvent B

The compounds according to the invention are prepared by the methods of synthesis described below, in which the substituents of the general formulae have the meanings specified hereinbefore. These methods are intended to illustrate the invention without restricting it to their content or limiting the scope of the compounds claimed to these Examples. Where the preparation of the starting compounds is not described, they are commercially obtainable or may be prepared analogously to known compounds or methods described herein. Substances described in the literature are prepared according to the published methods of synthesis.

Reaction scheme A



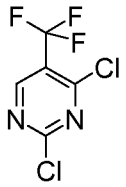
Example compounds of **type I** are prepared from 2,4-dichloropyrimidines **A-1** substituted by $\mathbf{R^5}$ in the 5 position, by nucleophilic aromatic substitution using one or more amines R^y-NH_2 and R^z-NH_2. The order of substitution depends to a great extent on the amines used, the reaction conditions (acidic or basic reaction conditions and the addition of Lewis acids) and the substituent R^5. R^y and R^z are in each case suitable groups for obtaining Example compounds according to the invention.

The nucleophilic aromatic substitutions at **A-1**, **A-2** and **A-3** are carried out according to methods known from the literature in common solvents, such as e.g. THF, DCM, NMP, EtOH, MeOH, DMSO or DMF using a base, such as for example DIPEA or K_2CO_3, or an acid, such as for example HCl. The amines used, R^yNH_2 and R^zNH_2, are commercially obtainable or are synthesised according to methods known from the literature. The diaminopyrimidines of **type I** which may be obtained directly by these methods may then be further modified in $\mathbf{R^y}$ and $\mathbf{R^z}$ in a manner known from or analogous to the literature to form further diaminopyrimidines of **type I**. Thus, for example, the groups $\mathbf{R^y}$ and $\mathbf{R^z}$ of directly obtainable diaminopyrimidines of **type I**, which consist of a carboxylic acid-, sulphonic acid-, halogen- or amino-substituted aryl, heteroaryl, cycloalkyl or heterocyloalkyl, may be modified by reactions of substitution (at the heteroaryl itself), alkylation, acylation, amination or addition.

Preparation of the starting compounds

Unless stated otherwise, all the starting materials are purchased from commercial suppliers and used directly in the syntheses. Substances described in the literature are prepared by the published methods of synthesis.

a) 2,4-dichloro-5-trifluoromethyl-pyrimidine (**A-1a**)



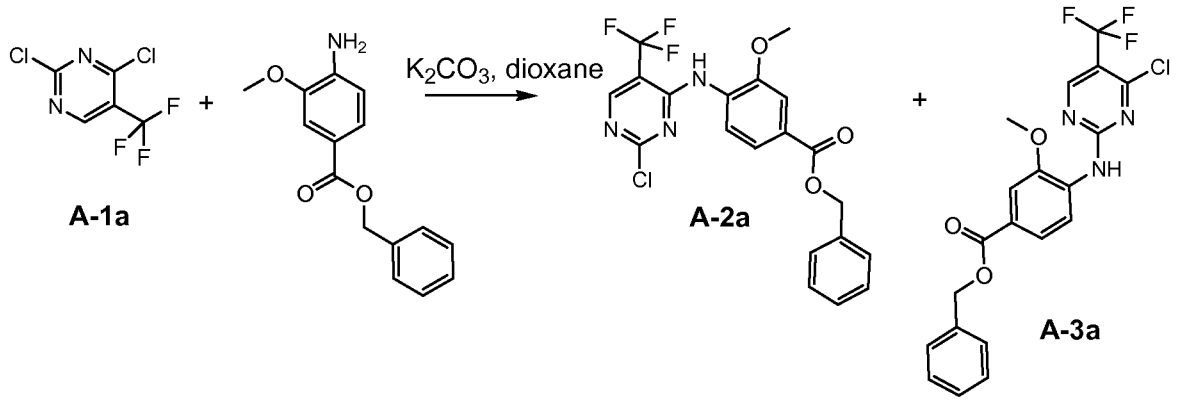
A-1a

5-trifluoromethyluracil (48.0 g, 267 mmol) is suspended in 210 mL phosphorus oxychloride ($POCl_3$) while moisture is excluded. Diethylaniline (47.7 g, 320 mmol) is slowly added dropwise to this suspension such that the temperature remains between 25°C and 30°C. After the addition has ended the mixture is stirred for a further 5 - 10 min in the water bath and the mixture is heated for 5 - 6 h with the exclusion of moisture at 80 - 90°C. The excess $POCl_3$ is destroyed by stirring into approx. 1200 g of sulphuric acid mixed with ice water and the aqueous phase is immediately extracted 3 x with in each case 500 mL diethyl ether or *tert.*-butylmethyl ether. The combined ethereal extracts are washed 2 x with 300 mL sulphuric acid mixed with ice water (approx. 0.1 M) and with cold saline solution and immediately dried on sodium sulphate. The desiccant is filtered off and the solvent is eliminated in vacuo. The residue is distilled in vacuo (10 mbar) through a short column (20 cm) (head temperature: 65 - 70°C), to obtain a colourless liquid that is bottled and stored under argon.

(TLC: R_f = 0.83 (in cHex:EA = 3:1)

Analogously to this procedure further pyrimidines **A-1** are obtained from the corresponding intermediates/educts or the corresponding commercially obtainable educt.

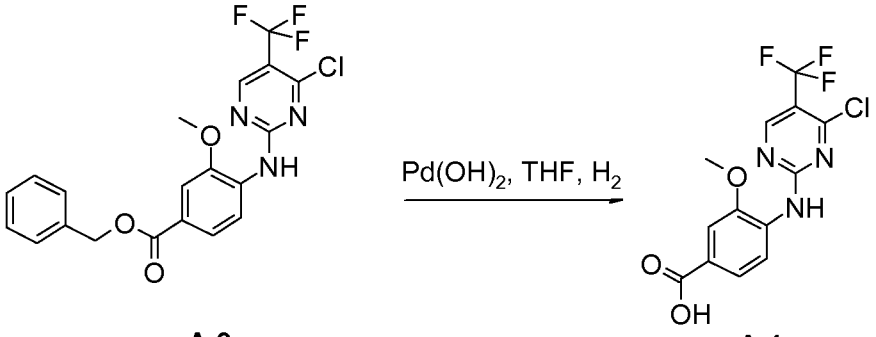
b) benzyl 4-(4-chloro-5-trifluoromethyl-pyrimidin-2-ylamino)-3-methoxy-benzoate **(A-3a)**



A-1a **A-2a** **A-3a**

Benzyl 4-amino-3-methoxybenzoate (1.92 g, 6.8 mmol) and K_2CO_3 (2.38 g, 17 mmol) are suspended in 4 mL dioxane and then mixed with 2,4-dichloro-5-trifluoromethylpyrimidine (1.48 mL, 6.8 mmol). The suspension is then refluxed for 100 min with stirring in the oil bath (approx. 130°C). Once the reaction has ended the reaction mixture is filtered, the filtrate is concentrated by rotary evaporation and purified by normal- phase column chromatography. The product-containing fractions of **A-3a** (HPLC-MS: $t_{Ret.}$ = 1.94 min; MS $(M-H)^-$ = 436) are combined and concentrated by rotary evaporation.

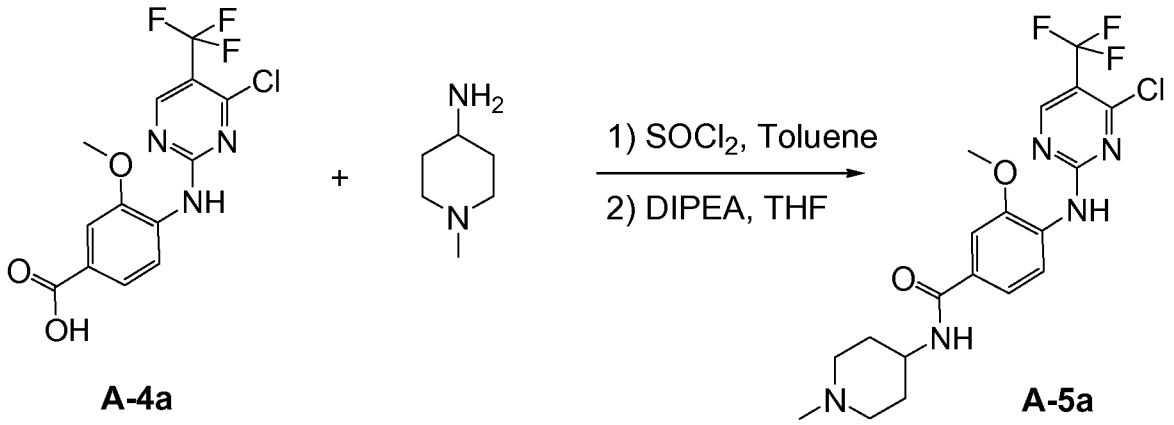
c) 4-(4-chloro-5-trifluoromethyl-pyrimidin-2-ylamino)-3-methoxy-benzoic acid (**A-4a**)



A-3a **A-4a**

Compound **A-3a** (1.3 g, 3 mmol) is suspended in a hydrogenating autoclave in 50 mL THF and mixed with $Pd(OH)_2$ on carbon (180 mg, charge 20 %, approx. 50 % water). Then 4.5 bar H_2 are pressed on and the reaction mixture is stirred for 24 h. After the reaction has ended the reaction mixture is filtered, the filtrate is evaporated down and the crude product **A-4a** (HPLC-MS: $t_{Ret.}$ = 1.24 min; MS $(M-H)^-$ = 346) is used in the subsequent reactions without any further purification.

d) 4-(4-chloro-5-trifluoromethyl-pyrimidin-2-ylamino)-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide (**A-5a**)



A-4a **A-5a**

Compound **A-4a** (2.0 g, 5.6 mmol) is suspended in 70 mL toluene, combined with thionyl chloride (840 µL, 11.5 mmol) and heated to 120°C for 2 h with stirring. The reaction mixture is allowed to cool to RT and the solvent is eliminated using the rotary evaporator. The residue is suspended in 50 mL THF, cooled to 0°C and a solution of 4-amino-1-methylpiperidine (657 mg, 5.75 mmol) and DIPEA (1.97 mL, 11.5 mmol), dissolved in 20 mL THF, is added dropwise. The reaction mixture is allowed to come slowly up to RT and stirred for a further 12 h at RT. The reaction mixture is cooled to 0°C, product **A-5a** is filtered off (HPLC-MS: $t_{Ret.}$ = 2.06 min; MS $(M+H)^+$ = 444) and used without further purification.

e) (1R,2*S*)-1-methanesulphonylamino-indan-2-yl methanesulphonate (**B-1a**)

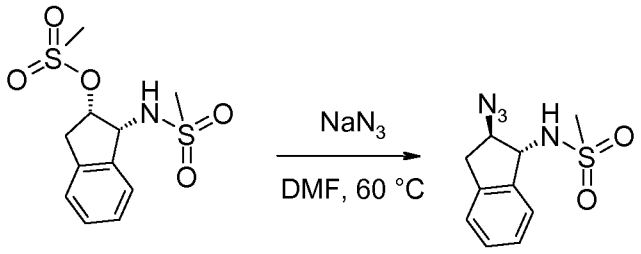


B-1a

(1R,2*S*)-1-amino-2-indanol (300 mg, 2.01 mmol) is in suspended 10 mL DCM, combined with triethylamine (1.68 mL, 12.1 mmol) and cooled to 0°C. Then methanesulphonic acid chloride (467 µL, 6.03 mmol) is added dropwise and the reaction mixture is left to warm up to RT. The reaction mixture is stirred for 1 h at RT and once the reaction is complete it is mixed with water and extracted with DCM. The organic phase is dried on $MgSO_4$, filtered,

the filtrate is evaporated down and the crude product **B-1a** (HPLC-MS: $t_{Ret.}$ = 1.03 min; MS $(M-H)^-$ = 304) is used in the subsequent reactions without further purification.

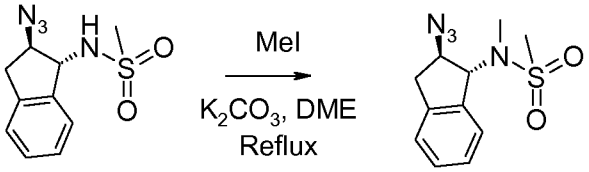
f) *N*-((1R,2*R*)-2-azido-indan-1-yl)-methanesulphonamide (**B-2a**)



B-1a **B-2a**

Compound **B-1a** (200 mg, 0.66 mmol) is suspended in 4 mL DMF, combined with NaN_3 (127 mg, 1.97 mmol) and heated to 60°C. The reaction mixture is stirred for 7 h and once the reaction is complete it is cooled to RT, mixed with water and extracted with DCM. The organic phase is dried on $MgSO_4$, filtered, the filtrate is evaporated down and the crude product **B-2a** (HPLC-MS: $t_{Ret.}$ = 1.25 min; MS $(M-H)^-$ = 251) is used in the subsequent reactions without further purification.

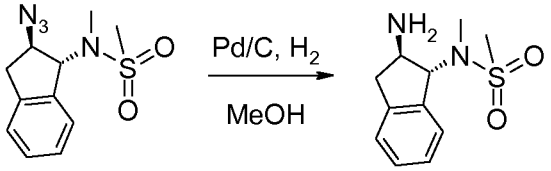
g) *N*-((1R,2*R*)-2-azido-indan-1-yl)-*N*-methyl-methanesulphonamide (**B-3a**)



B-2a **B-3a**

Compound **B-2a** (100 mg, 0.39 mmol) is suspended in 5 mL DME, mixed with K_2CO_3 (110 mg, 0.79 mmol) and MeI (75 µL, 1.19 mmol) and heated to 85°C. The reaction mixture is stirred overnight, once the reaction is complete it is cooled to RT, mixed with water and extracted with EtOAc. The organic phase is dried on $MgSO_4$, filtered, the filtrate is evaporated down and the crude product **B-3a** (HPLC-MS: $t_{Ret.}$ = 1.35 min) is used in the subsequent reactions without further purification.

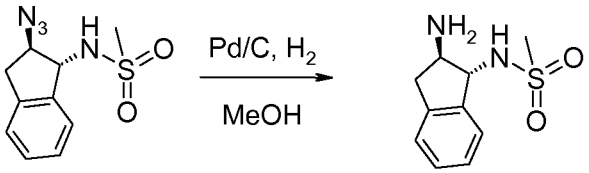
h) *N*-((1R,2*R*)-2-amino-indan-1-yl)-*N*-methyl-methanesulphonamide (**B-4a**)



B-3a **B-4a**

Compound **B-3a** (100 mg, 0.38 mmol) is suspended in a hydrogenating autoclave in 20 mL MeOH and mixed with Pd on charcoal (50 mg, load 10 %). Then 4 bar H_2 is pressed in and the reaction mixture is stirred for 24 h. After the reaction has ended the reaction mixture is filtered, the filtrate is evaporated down and the crude product **B-4a** (HPLC-MS: $t_{Ret.}$ = 1.03 min; MS $(M+H)^+$ = 241) is used in the subsequent reactions without further purification.

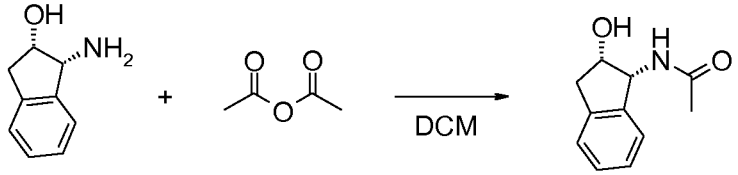
i) *N*-((1R,2*R*)-2-amino-indan-1-yl)-methanesulphonamide (**B-5a**)



B-2a **B-5a**

Compound **B-2a** (1.5 g, 5.95 mmol) is suspended in 100 mL MeOH in a hydrogenating autoclave and combined with Pd on charcoal (250 mg, charge 10 %). Then 4 bar H_2 is pressed in and the reaction mixture is stirred for 24 h. After the reaction has ended the reaction mixture is filtered, the filtrate is evaporated down and the crude product **B-5a** (HPLC-MS: $t_{Ret.}$ = 0.2 min; MS $(M+H)^+$ = 227) is used in the subsequent reactions without further purification.

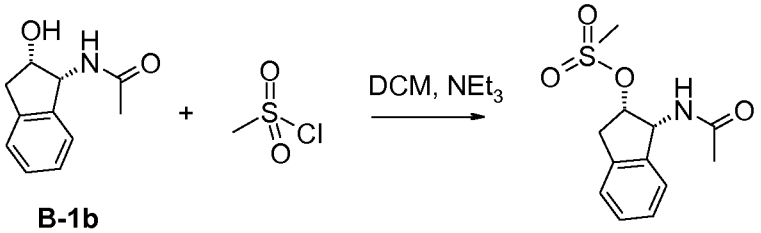
j) *N*-((1R,2*S*)-2-hydroxy-indan-1-yl)-acetamide (**B-1b**)



B-1b

(1R,2*S*)-1-amino-2-indanol (2.0 g, 13.4 mmol) is suspended in 100 mL DCM and at RT it is combined with acetic anhydride (1.27 mL, 13.4 mmol). The reaction mixture is stirred for 1 h at RT, once the reaction is complete the solvent is eliminated using the rotary evaporator and the crude product **B-1b** (HPLC-MS: $t_{Ret.}$ = 0.81 min; MS $(M+H)^+$ = 192) is used in the subsequent reactions without further purification.

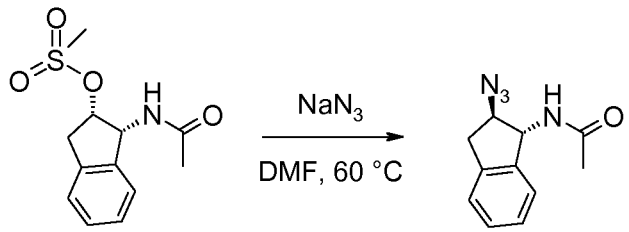
k) (1R,2*S*)-1-acetylamino-indan-2-yl methanesulphonate (**B-2b**)



B-1b **B-2b**

Compound **B-1b** (2.56 g, 13.39 mmol) is suspended in 100 mL DCM, cooled to 0°C and then mixed with triethylamine (5.60 mL, 40.2 mmol) and methanesulphonic acid chloride (1.56 mL, 20.1 mmol). The reaction mixture is stirred for 1 h at 0°C, once the reaction is complete it is mixed with water and extracted with EtOAc. The organic phase is dried on $MgSO_4$, filtered, the filtrate is evaporated down and the crude product **B-2b** (HPLC-MS: $t_{Ret.}$ = 0.99 min; MS $(M+H)^+$ = 270) is used in the subsequent reactions without further purification.

l) *N*-((1R,2*R*)-2-azido-indan-1-yl)-acetamide (**B-3b**)

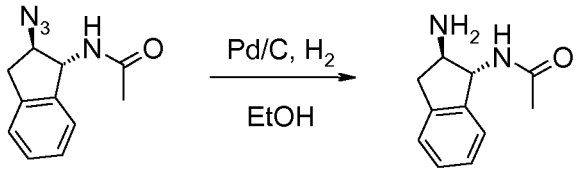


B-2b **B-3b**

Compound **B-2b** (3.50 g, 12.99 mmol) is suspended in 73 mL DMF, combined with NaN_3 (2.54 g, 38.99 mmol) and heated to 60°C. The reaction mixture is stirred for 16 h, once the reaction is complete it is cooled to RT and mixed with 500 mL water and 50 mL saturated $NaHCO_3$ solution. The mixture is stirred for 30 min and the precipitated solid is filtered off

and dried. The crude product **B-3b** (HPLC-MS: $t_{Ret.}$ = 1.11 min; MS $(M+H)^+$ = 217) is used in the subsequent reactions without further purification.

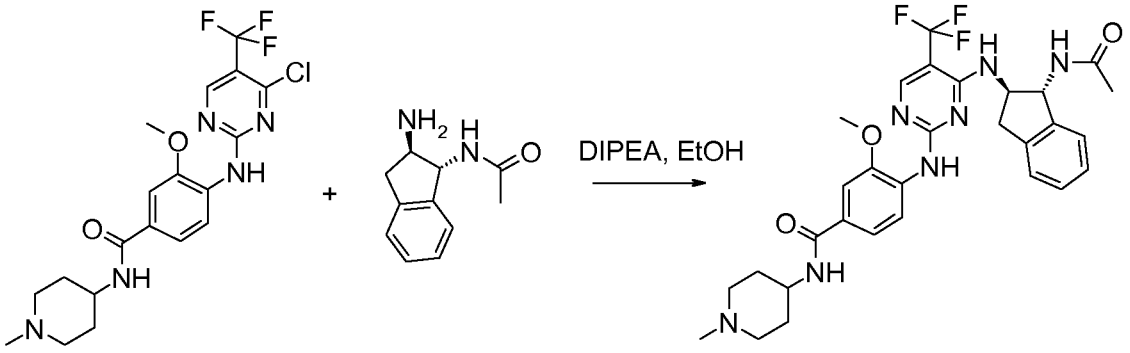
m) *N*-((1R,2*R*)-2-amino-indan-1-yl)-acetamide (**B-4b**)



B-3b **B-4b**

Compound **B-3b** (1.89 g, 8.74 mmol) is suspended in 200 mL EtOH in a hydrogenating autoclave and combined with Pd on charcoal (200 mg, charge 10 %). Then 5 bar H_2 are pressed in and the reaction mixture is stirred for 4 h. After the reaction has ended the reaction mixture is filtered, the filtrate is evaporated down and the crude product **B-4b** (HPLC-MS: $t_{Ret.}$ = 0.19 min; MS $(M+H)^+$ = 191) is used in the subsequent reactions without further purification.

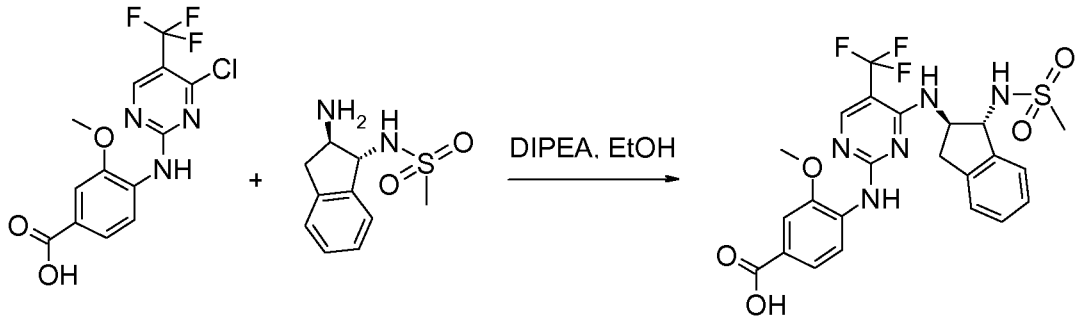
n) 4-[4-((1R,2*R*)-1-acetylamino-indan-2-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide (**I-1**)



A-5a **B-4b** **I-1**

Compound **A-5a** (70 mg, 0.16 mmol) and *N*-((1R,2*R*)-2-amino-indan-1-yl)-acetamide (**B-4b**) (33 mg, 0.17 mmol) are suspended in 700 µL EtOH, mixed with DIPEA (104 µL, 0.63 mmol) and stirred overnight at 75°C. The reaction mixture is left to cool to RT and the solvent is eliminated using the rotary evaporator. The residue is taken up in DMF and purified by preparative HPLC. The product-containing fractions of **I-1** (HPLC-MS: $t_{Ret.}$ = 1.82 min; MS $(M+H)^+$ = 598) are freeze-dried.

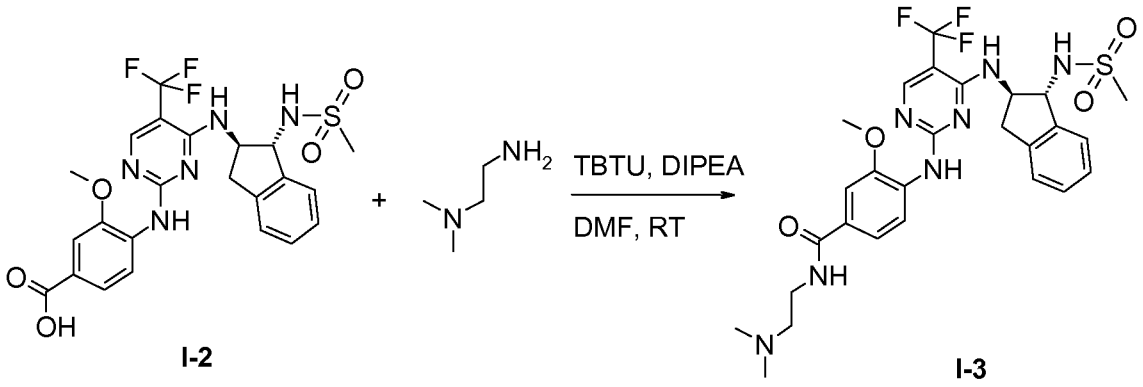
o) 4-[4-((1R,2*R*)-1-methanesulphonylamino-indan-2-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-3-methoxy-benzoic acid (**I-2**)



A-4a **B-5a** **I-2**

Compound **A-4a** (307 mg, 0.88 mmol) and *N*-((1R,2*R*)-2-amino-indan-1-yl)-methanesulphonamide **B-5a** (200 mg, 0.88 mmol) are suspended in 5 mL EtOH, combined with DIPEA (1.13 mL, 2.65 mmol) and stirred overnight at 70°C. The reaction mixture is left to cool to RT and the solvent is eliminated using the rotary evaporator. The residue is taken up in DMF and purified by preparative HPLC. The product-containing fractions of **I-2** (HPLC-MS: $t_{Ret.}$ = 1.42 min; MS $(M+H)^+$ = 538) are freeze-dried.

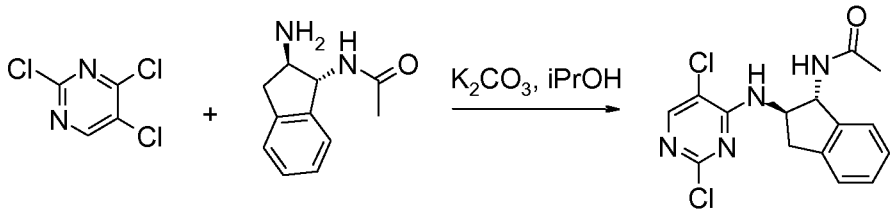
p) *N*-(2-dimethylamino-ethyl)-4-[4-((1R,2*R*)-1-methanesulphonylamino-indan-2-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-3-methoxy-benzamide (**I-3**)



I-2 **I-3**

Pyrimidine **I-2** (70 mg, 0.13 mmol) and TBTU (42 mg, 0.13 mmol) are suspended in DMF (500 µL), mixed with DIPEA (74 µL, 0.43 mmol) and the reaction mixture is stirred for 15 min at RT. Then N^1,N^1-dimethylethan-1,2-diamine (15 mg, 0.15 mmol) is added and the reaction mixture is stirred overnight. The reaction mixture is filtered and purified by preparative HPLC. The product-containing fractions of **I-3** (HPLC-MS: $t_{Ret.}$ = 1.83 min; MS $(M+H)^+$ = 608) are freeze-dried.

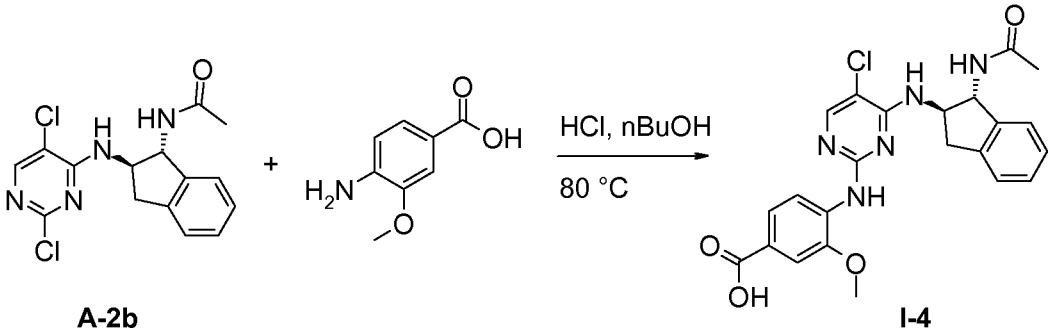
g) *N*-[(1R,2*R*)-2-(2,5-dichloro-pyrimidin-4-ylamino)-indan-1-yl]-acetamide (**A2-b**)



A-1b **B-4b** **A-2b**

2.4,5-trichloropyrimidine (500 mg, 2.73 mmol) is suspended in 35 mL *iso*-PrOH and combined with K_2CO_3 (5.28 g, 38.16 mmol). Then *N*-((1R,2*R*)-2-amino-indan-1-yl)-acetamide **B-4b** (570 mg, 2.99 mmol) is added and the reaction mixture is stirred for 3 h at 55°C. The reaction mixture is evaporated down, mixed with water and extracted with EtOAc. The organic phase is dried on magnesium sulphate and evaporated down in vacuo. The crude product of **A-2b** (HPLC-MS: $t_{Ret.}$ = 1.24 min; MS $(M+H)^+$ = 337/339) is used in the subsequent reactions without further purification.

r) 4-[4-((1R,2*R*)-1-acetylaminoindan-2-ylamino)-5-chloro-pyrimidin-2-ylamino]-3-methoxy-benzoic acid (**I-4**)



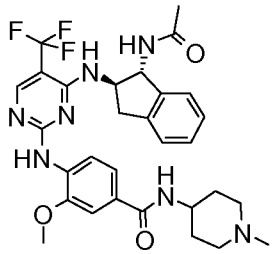
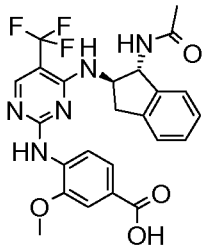
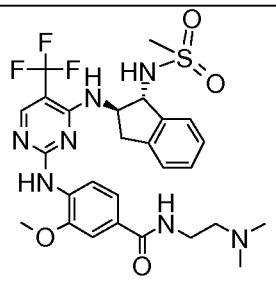
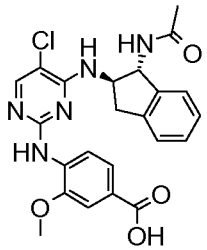
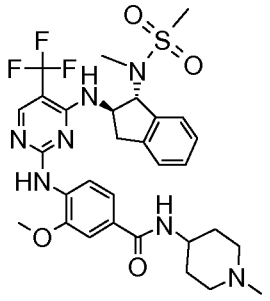
A-2b **I-4**

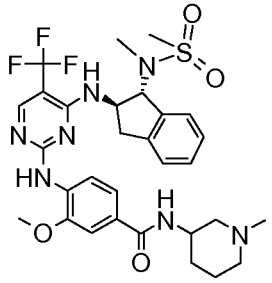
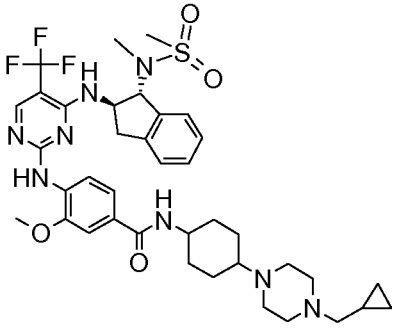
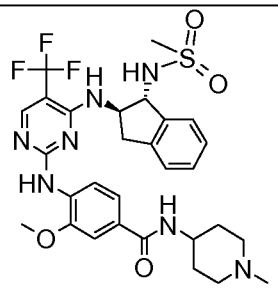
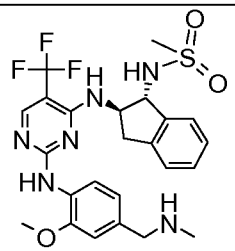
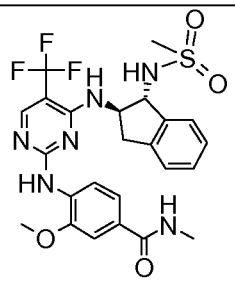
Pyrimidine **A-2b** (928 mg, 2.75 mmol) and 3-methoxy-4-aminobenzoic acid (690 mg, 4.13 mmol) are suspended in *n*-BuOH (10 mL), combined with HCl in dioxane (137 µL, 0.55 mmol, 4 M) and the reaction mixture is heated to 150°C in a microwave reactor for 20 min. After the reaction has ended all the volatile constituents are eliminated in vacuo, the reaction mixture is combined with DMF and purified by preparative HPLC. The product-containing fractions of **I-4** (HPLC-MS: $t_{Ret.}$ = 1.20 min; MS $(M+H)^+$ = 468/470) are freeze-dried.

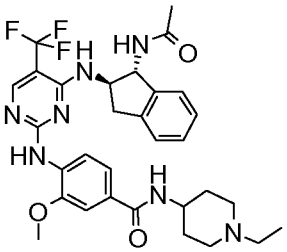
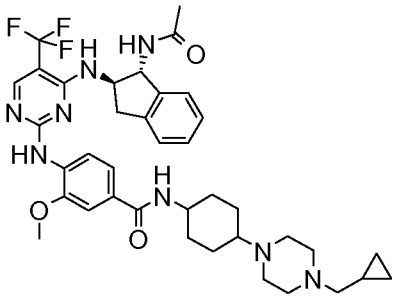
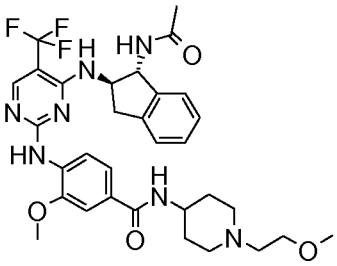
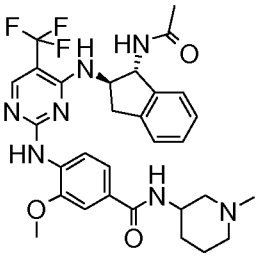
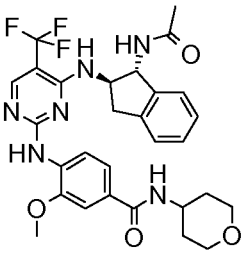
Analogously to reaction methods a) to r) described above for the synthesis of Examples **I-1** to **I-4**, the following Examples **I-4** to **I-98** (Table 1) and comparable other examples

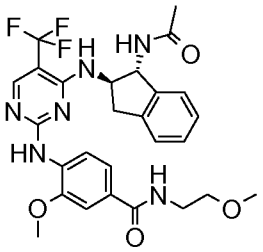
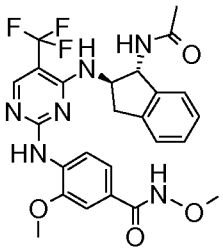
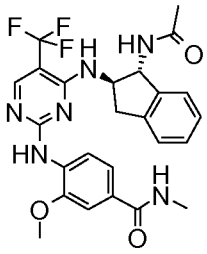
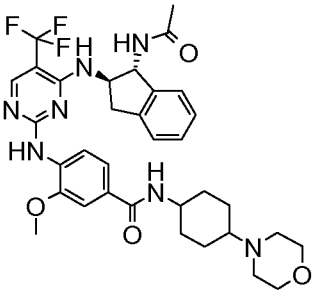
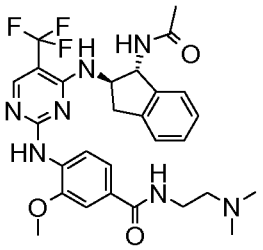
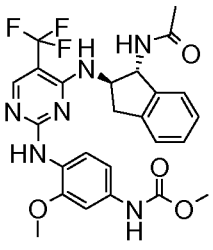
may also be obtained from the corresponding precursors, which are either commercially obtainable or prepared by methods known from the literature.

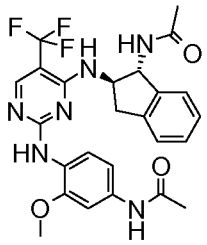
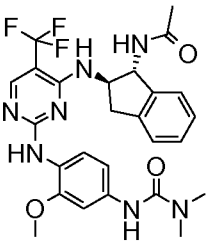
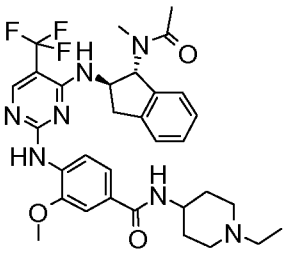
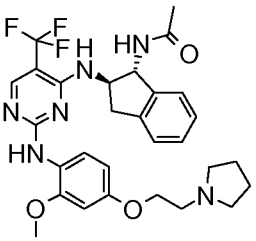
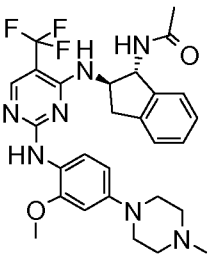
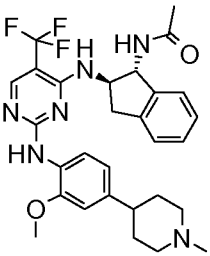
Table 1

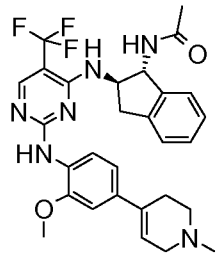
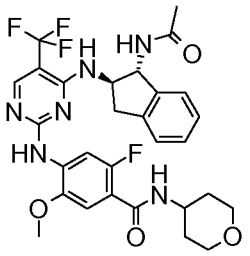
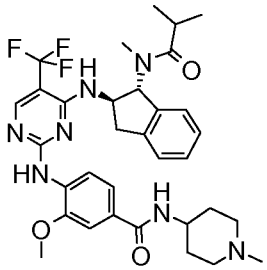
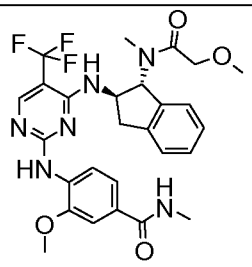
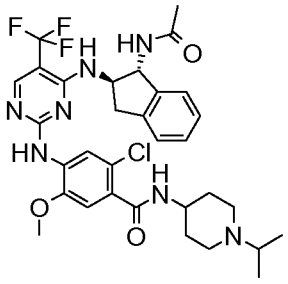
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-1		1.82	598
I-2		1.43	502
I-3		1.83	608
I-4		1.20	468
I-5		1.90	648

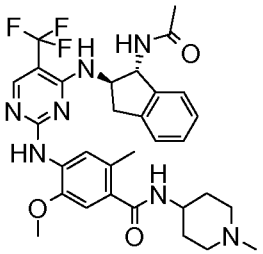
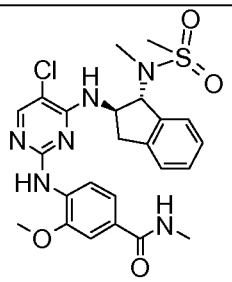
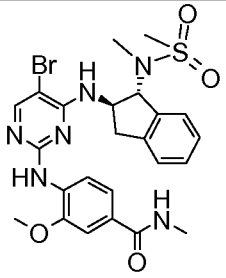
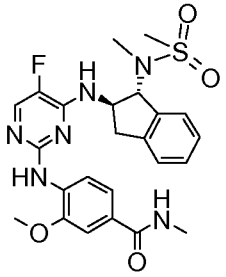
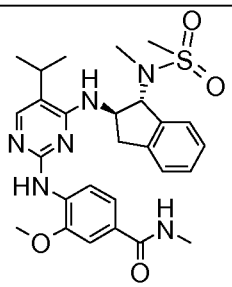
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I-6		1.98	648
I-7		2.03	771
I-8		1.83	634
I-9		1.92	537
I-10		1.76	551

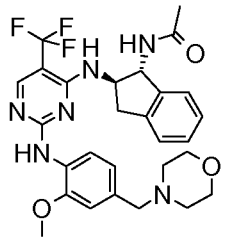
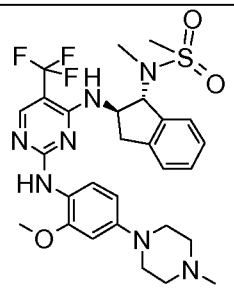
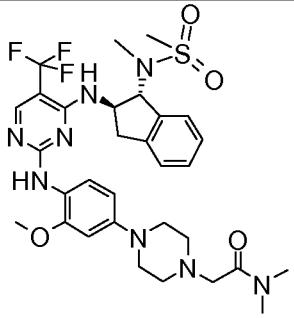
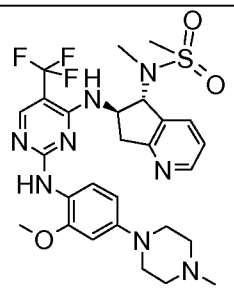
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-11		1.89	612
I-12		1.97	721
I-13		1.81	642
I-14		1.90	598
I-15		1.77	585

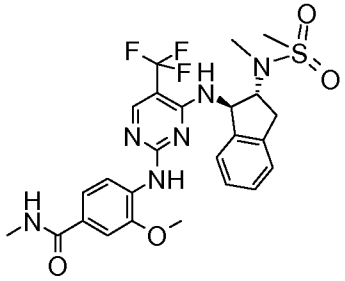
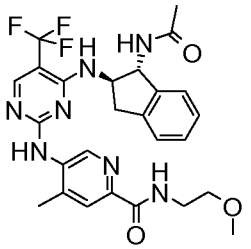
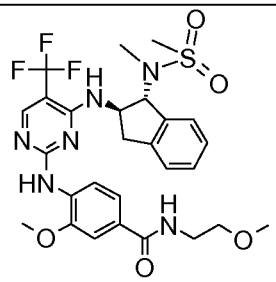
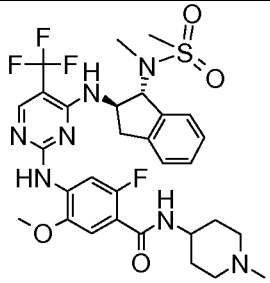
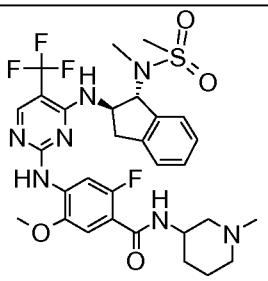
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I-16		1.76	559
I-17		1.45	531
I-18		1.71	515
I-19		1.83	668
I-20		1.79	572
I-21			

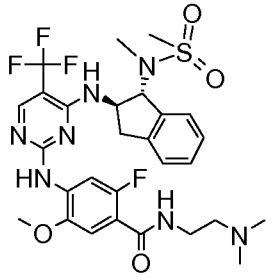
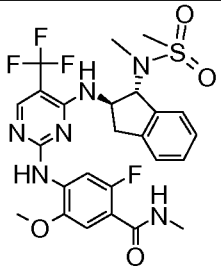
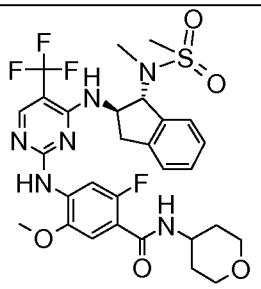
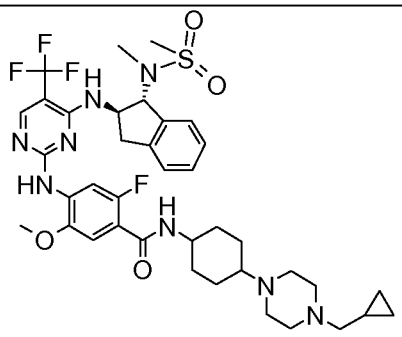
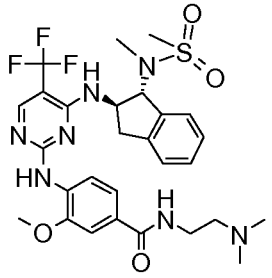
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-22			
I-23			
I-24			
I-25			
I-26		1.85	556
I-27			

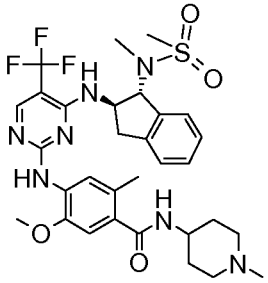
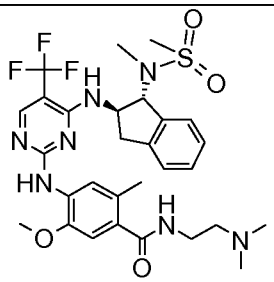
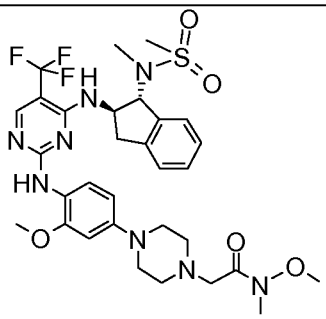
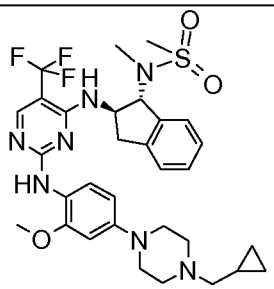
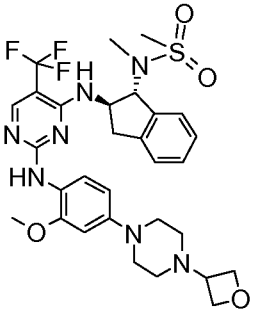
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-28			
I-29			
I-30			
I-31			
I-32			

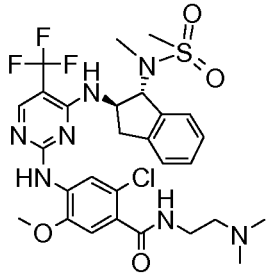
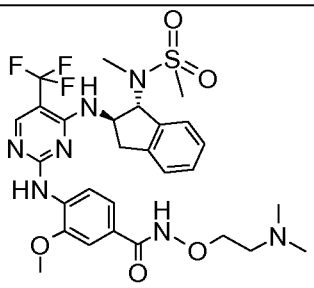
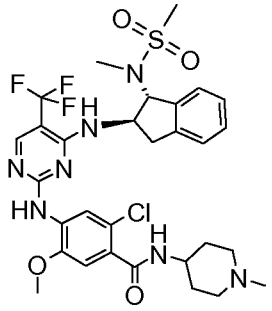
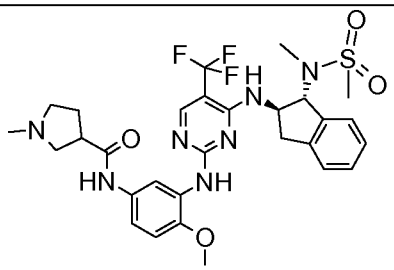
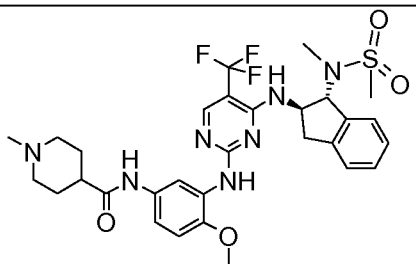
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-33			
I-34		1.77	531
I-35			
I-36			
I-37			

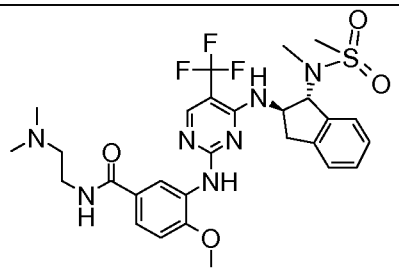
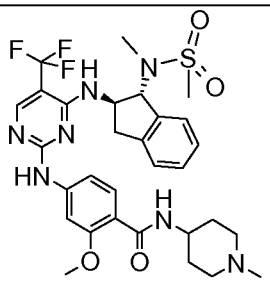
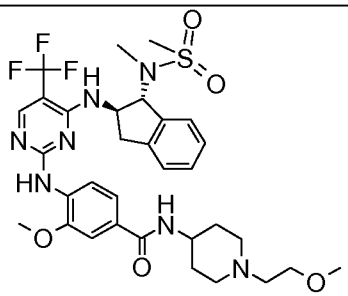
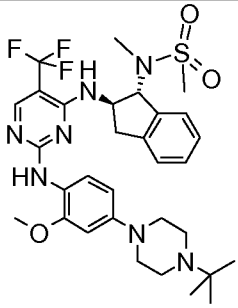
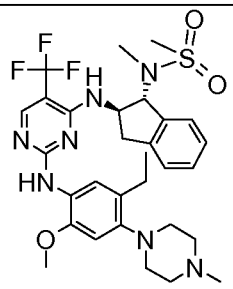
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-38		1.89	557
I-39		2.12	606
I-40		1.90	677
I-41			
I-42			

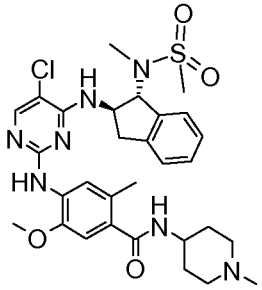
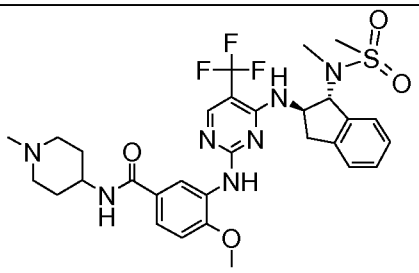
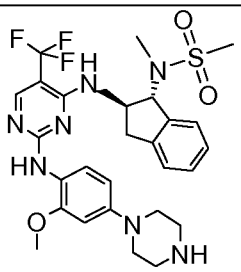
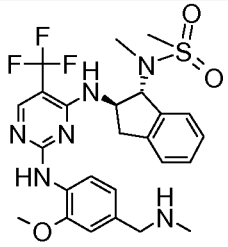
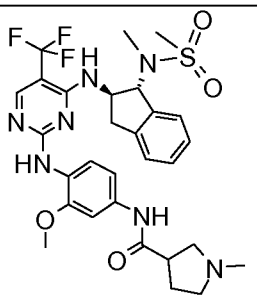
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-43			
I-44			
I-45		1.87	609
I-46		2.01	666
I-47		2.11	666

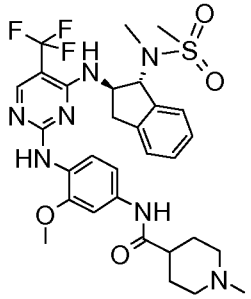
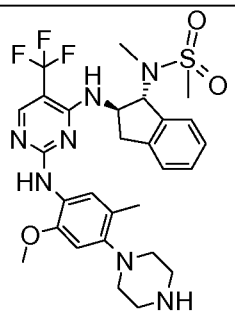
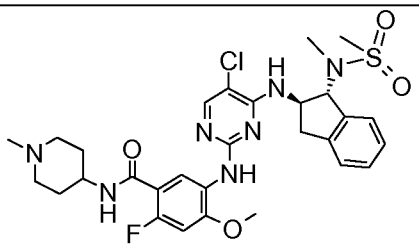
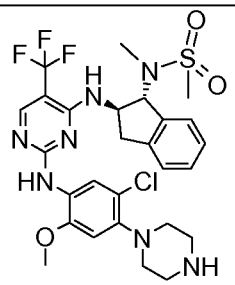
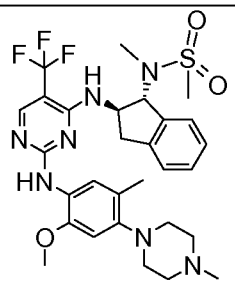
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-48		2.01	640
I-49		1.94	583
I-50		1.99	653
I-51		2.18	789
I-52		1.87	622

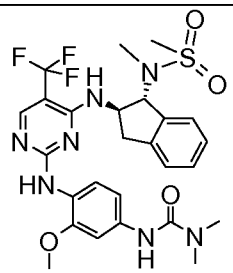
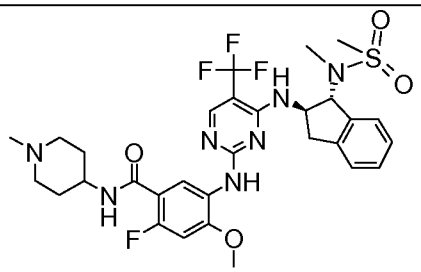
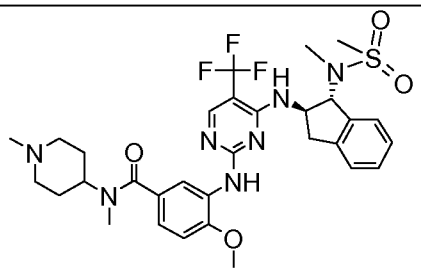
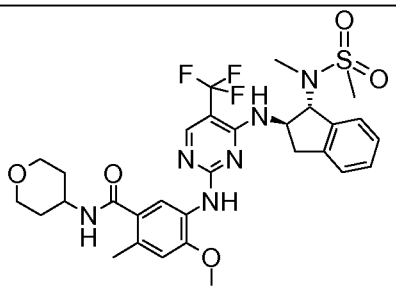
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-53		1.88	662
I-54		1.90	636
I-55		1.90	677
I-56		2.19	646
I-57		1.89	648

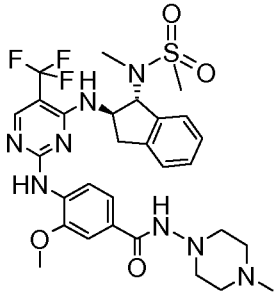
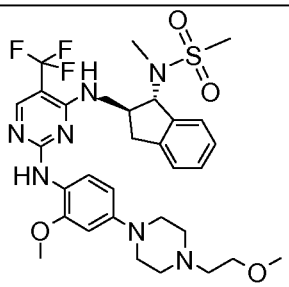
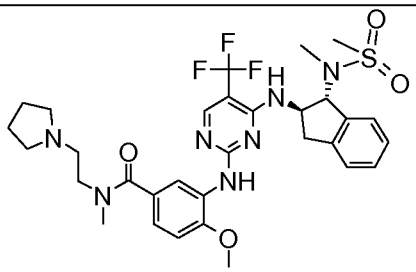
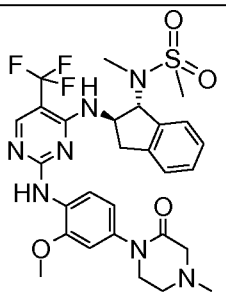
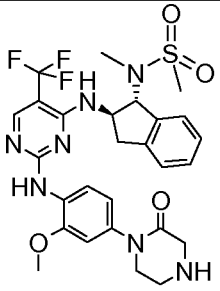
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-58		1.96	656
I-59		1.77	638
I-60		1.93	682
I-61		1.91	634
I-62		1.90	648

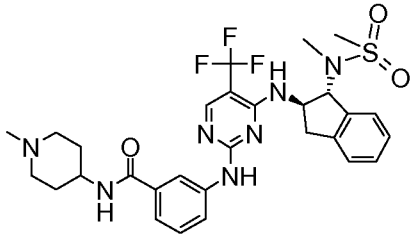
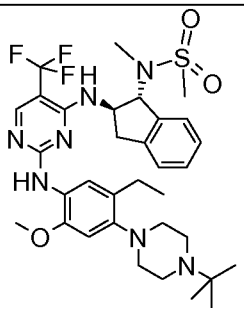
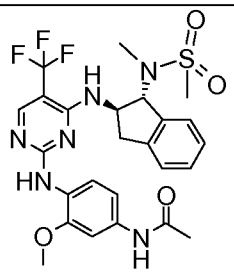
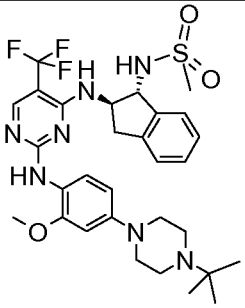
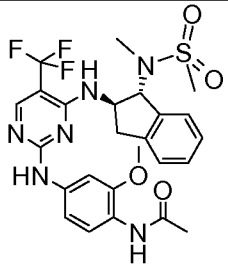
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-63		1.97	622
I-64		1.85	648
I-65		1.89	692
I-66		2.25	648
I-67		2.26	634

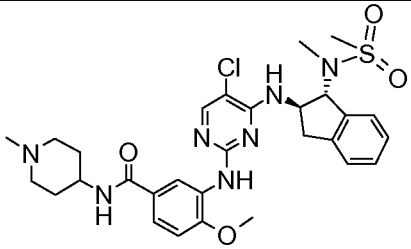
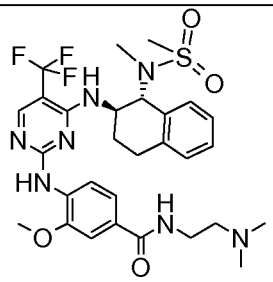
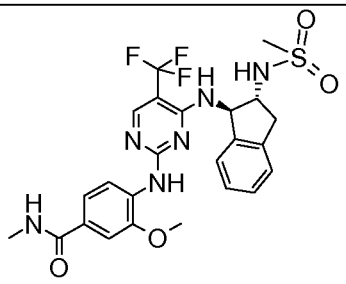
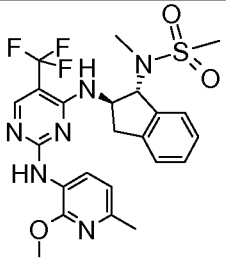
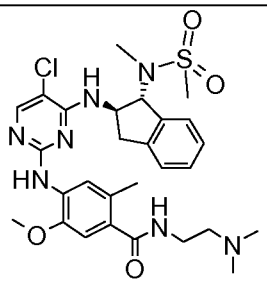
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-68		1.82	628
I-69		1.87	648
I-70		1.82	592
I-71		2.00	551
I-72		1.92	634

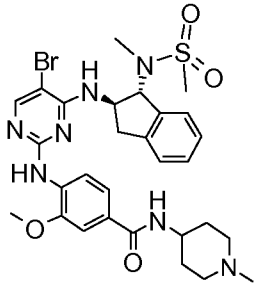
#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-73		1.90	648
I-74		2.05	606
I-75		1.86	632/634
I-76		2.09	626
I-77		2.17	620

#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-78		2.45	662
I-79		1.85	594
I-80		2.08	666
I-81		1.90	662
I-82		1.85	647 (M-H)

#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-83		1.75	649
I-84		1.99	650
I-85		2.02	662
I-86		1.81	620
I-87		1.77	606

#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-88		1.82	618
I-89		2.53	676
I-90		1.80	565
I-91		2.19	634
I-92		1.78	565

#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-93		1.80	614
I-94		1.91	636
I-95		1.75	551
I-96		2.19	523
I-97		1.84	602/604

#	Structure	t_{Ret} (HPLC) [min]	MS $(M+H)^+$
I-98		1.82	658/660

The following Examples describe the biological activity of the compounds according to the invention without restricting the invention to these Examples.

PTK2 Enzyme tests

Assay 1

This test uses active PTK2 enzyme (Invitrogen Code PV3832) and poly-Glu-Tyr (4:1, Sigma P-0275) as the kinase substrate. The kinase activity is detected through the phosphorylation of the substrate in a DELFIA™ assay. The phosphorylated substrate is detected with the europium-labelled phosphotyrosine antibody PT60 (Perkin Elmer, No.: AD00400).

In order to determine concentration-activity curves with PTK2-inhibitors the compounds are serially diluted in 10 % DMSO/H_2O and 10 µL of each dilution are placed in each well of a 96-well microtitre plate (clear plate with a U-shaped base, Greiner No. 650101) (the inhibitors are tested in duplicates) and mixed with 10 µL/well of PTK2 kinase (0.01 µg/well). PTK2 kinase has been correspondingly diluted beforehand with kinase dilution buffer (20 mM TRIS/HCl pH 7.5, 0.1 mM EDTA, 0.1 mM EGTA, 0.286 mM sodium orthovanadate, 10 % glycerol with the addition of freshly prepared BSA (fraction V, 1 mg/mL) and DTT (1 mM)). The test compound and the PTK2 kinase are pre-incubated for 1 h at RT and shaken at 500 revolutions per min. The reaction is started by the addition of 10 µL/well poly (Glu,Tyr) substrate (25 µg/well poly (Glu, Tyr), 0.05 µg/well biotinylated poly (Glu,Tyr) dissolved in 250 mM TRIS/HCl pH 7.5, 9 mM DTT)– the final concentration of DMSO is 2 %. Then 20 µL of ATP Mix (30 mM TRIS/HCl pH 7.5, 0.02 % Brij, 0.2 mM sodium orthovanadate, 10 mM magnesium acetate, 0.1 mM EGTA, 1x phosphatase inhibitor cocktail 1 (Sigma, No.: P2850), 50 µM ATP (Sigma, No.: A3377; 15 mM stock solution)) are added. After 1 h of kinase reaction (the plates are shaken at 500 rpm), the reaction is stopped by the addition of 12 µL/well 100 mM EDTA, pH 8.0 and

shaken for a further 5 min at RT (500 rpm). 55 µL of the reaction mixture are transferred into a streptavidin plate (Strepta Well High Bind (transparent, 96-well) made by Roche, No.: 11989685001) and incubated for 1 h at RT (shaking at 500 rpm). Then the microtitre plate is washed three times with 200 µL/well D-PBS (Invitrogen, No. 14190). 100 µL of a solution containing DELFIA Eu-N1 Anti-Phosphotyrosine PT60 antibody (Perkin Elmer, No.: AD0040, diluted 1:2000 in DELFIA test buffer (Perkin Elmer, No.: 1244-111)) is then added and the mixture is incubated for 1 h at RT (shaking at 500 rpm). Then the plate is washed three times with 200 µL/well DELFIA washing buffer (Perkin Elmer, No.: 1244-114), 200 µL/well strengthening solution (Perkin Elmer, No.: 1244-105) are added and the mixture is incubated for 10 min at RT (shaking at 300 rpm).

The time-delayed europium fluorescence is then measured in a microtitre plate reader (VICTOR^3, Perkin Elmer). The positive controls used are wells that contain the solvent controls (2 % DMSO in test buffer) and exhibit uninhibited kinase activity. Wells that contain test buffer instead of enzyme are used as a control of the background kinase activity.

The IC_{50} values are determined from analyses of the concentration activity by iterative calculation with the aid of a sigmoid curve analysis algorithm (FIFTY, based on GraphPAD Prism Version 3.03) with a variable Hill coefficient.

Assay 2

This test uses active PTK2 enzyme (Invitrogen Code PV3832) and poly-Glu-Tyr (4:1, Sigma P-0275) as the kinase substrate. The kinase activity is detected by means of the phosphorylation of the substrate in a DELFIA^{TM} assay. The phosphorylated substrate is detected with the europium-labelled phosphotyrosine antibody PT66 (Perkin Elmer, No.: AD0040).

In order to determine concentration-activity curves with PTK2-inhibitors the compounds are serially diluted first of all in 100 % DMSO and then in kinase dilution buffer (20 mM TRIS/HCl pH 7.5, 0.1 mM EDTA, 0.1 mM EGTA, 0.286 mM sodium orthovanadate, 10 % glycerol with the addition of freshly prepared BSA (fraction V, 1 mg/mL) and DTT (1 mM)) and 10 µL of each dilution are dispensed per well in a 96-well microtitre plate (clear U-shaped base plate, Greiner No. 650101) (the inhibitors are tested in duplicates) and mixed with 10 µL/well of PTK2 kinase (0.01 µg/well). PTK2 kinase is diluted accordingly beforehand with kinase dilution buffer. The diluted PTK2 inhibitor and the PTK2 kinase

are pre-incubated for 1 h at RT and shaken at 500 revolutions per min. Then 10 µL/well poly-Glu-Tyr substrate (25 µg/well poly-Glu-Tyr, 0.05 µg/well biotinylated poly-Glu-Tyr dissolved in 250 mM TRIS/HCl pH 7.5, 9 mM DTT) are added. The reaction is started by the addition of 20 µL of ATP Mix (30 mM TRIS/HCl pH 7.5, 0.02 % Brij, 0.2 mM sodium orthovanadate, 10 mM magnesium acetate, 0.1 mM EGTA, 1x phosphatase inhibitor cocktail 1 (Sigma, No.: P2850), 50 µM ATP (Sigma, No.: A3377; 15 mM stock solution)) - the final concentration of DMSO is 0.5 %. After 1 h kinase reaction (the plates are shaken at 500 rpm), the reaction is stopped by the addition of 12 µL/well of 100 mM EDTA, pH 8, and shaken for a further 5 min at RT (500 U/min). 55 µL of the reaction mixture are transferred into a streptavidin plate (Strepta Well High Bind (transparent, 96-well) made by Roche, No.: 11989685001) and incubated for 1 h at RT (shaking at 500 rpm). Then the microtitre plate is washed five times with 200 µL/well D-PBS (Invitrogen, No. 14190). 100 µL of a solution containing DELFIA Eu-N1 Anti-Phosphotyrosine PT66 antibody (Perkin Elmer, No.: AD0040, diluted 1:9000 in DELFIA test buffer (Perkin Elmer, No.: 1244-111)) is then added and it is incubated for 1 h at RT (shaking at 500 rpm). Then the plate is washed five times with 200 µL/well DELFIA washing buffer (Perkin Elmer, No.: 1244-114), 200 µL/well strengthening solution (Perkin Elmer, No.: 1244-105) is added and the whole is incubated for 10 min at RT (shaking at 300 rpm).

The time-delayed europium fluorescence is then measured in a microtitre plate reader (VICTOR^3, Perkin Elmer). The positive control consists of wells that contain solvent (0.5 % DMSO in test buffer) and display uninhibited kinase activity. Wells that contain test buffer instead of enzyme act as a control for the background kinase activity.

The IC_{50} values are determined from concentration-activity analyses by iterative calculation using a sigmoid curve analysis algorithm (FIFTY, based on GraphPAD Prism Version 3.03) with a variable Hill coefficient.

Table 2 that follows gives the IC_{50} values of representative Example Compounds of type I as obtained by determining from Assay 1 or Assay 2 (*). The inhibitory activity of the compounds according to the invention is thus demonstrated sufficiently.

Table 2

#	PTK2 1h IC_{50} [nM]
I-1	2
I-3	2
I-5	2
I-6	0.96
I-7	1
I-8	2
I-9	2
I-10	2
I-11	2
I-12	4
I-13	3
I-14	2
I-15	4
I-16	2
I-17	2
I-18	2
I-19	3
I-20	1
I-26	2
I-34	7
I-38	2
I-39	3
I-40	3
I-45	2
I-46	2
I-47	3

#	PTK2 1h IC_{50} [nM]
I-48	1
I-49	6
I-50	8
I-51	4
I-52	1
I-53	1
I-54	0.84
I-55	4
I-56	3
I-57	3
I-58	4
I-59	0.83
I-60	1
I-61	0.43*
I-62	0.62*
I-63	0.71*
I-64	0.76
I-65	1
I-66	0.6*
I-67	0.68*
I-68	1
I-69	0.37*
I-70	0.98
I-71	1
I-72	0.74*
I-73	0.48*

#	PTK2 1h IC_{50} [nM]
I-74	0.66*
I-75	0.3*
I-76	0.76*
I-77	0.56*
I-78	0.83*
I-79	0.23*
I-80	0.36*
I-81	0.43*
I-82	0.36*
I-83	0.47*
I-84	1
I-85	0.44*
I-86	0.31*
I-87	0.48*
I-88	0.26*
I-89	0.68*
I-90	3
I-91	0.75*
I-92	2
I-93	0.6*
I-94	16*
I-95	6
I-96	11
I-97	2
I-98	1

Soft-Agar Assay

This cellular test is used to determine the influence of PTK2-inhibitors on the growth of PC-3 prostate carcinoma cells in soft agar ('anchorage-independent growth'). After an incubation time of two weeks the cell vitality is demonstrated by Alamar Blue (resazurin) staining.

PC-3 cells (ATCC CRL-1435) are grown in cell culture flasks (175 cm^2) with F12 Kaighn's Medium (Gibco, No.: 21127) which has been supplemented with 10 % foetal calf serum (Invitrogen, No.: 16000-044). The cultures are incubated in the incubator at 37°C and 5 % CO_2 and are run twice a week. The test I carried out in 96-well microtitre plates (Greiner, No.: 655 185) and consists of a lower layer made up of 90 µL of medium with 1.2 % agarose (Invitrogen, 4 % agarose gel 1x liquid 40 mL, No.: 18300-012), followed by a cell layer in 60 µL medium and 0.3 % agarose and finally a top layer comprising 30 µL

medium which contains the test compounds (without the addition of agarose). To prepare the lower layer, 4 % agarose are decocted with 10x D-PBS (Gibco, No.: 14200) and H_2O and thus prediluted on 3 % agarose in 1 x D-PBS. The latter is adjusted with culture medium (F12 Kaighn's /10 % FCS) and FCS to a final dilution of 1.2 % agarose in F12 Kaighn's Medium with 10 % FCS. Each well of a microtitre plate is supplied with 90 µL of the suspension for the lower layer and cooled to RT for 1 h. For the cell layer, PC-3 cells are detached using trypsin (Gibco, 0.05 %; No.: 25300), counted and 400 cells in each case seeded in 60 µL F12 Kaighn's (10 % FCS) with the addition of 0.3 % agarose per well (37°C). After cooling to RT for 2 h the test compounds (30 µL from serial dilutions) are added for triple measurements. The concentration of the test compounds usually covers a test range of between 1 µM and 0.06 nM. The compounds (stock solution: 10 mM in 100 % DMSO) are prediluted in F12 Kaighn's Medium, to obtain a final concentration of 0.8 % DMSO. The cells are incubated at 37°C and 5 % CO_2 in a steam-saturated atmosphere for 14 days. The metabolic activity of living cells is then demonstrated with the dye Alamar Blue (AbD Serotec, No.: BUF012B). To do this, 25 µL/well of an Alamar Blue suspension are added and the whole is incubated for approx. 8 h in the incubator at 37°C. The positive control consists of empty wells that are filled with a mixture of 25 µL of Alamar Blue reduced by autoclaving and 175 µL of F12 Kaighn's Medium (10 % FCS). The negative control used is a well that contains the two agarose layers without cells and the top layer of medium. The fluorescence intensity is determined by means of a fluorescence spectrometer (SpectraMAX GeminiXS, Molecular Devices). The excitation wavelength is 530 nm, the emission wavelength is 590 nm.

The EC_{50} values are determined from concentrations-activity analyses by iterative calculation using a sigmoid curve analysis algorithm (FIFTY, based on GraphPAD Prism Version 3.03) with a variable Hill coefficient.

Phospho-PTK2 (pY397) Assay

This cellular test is used to determine the influence of PTK2-inhibitors on the state of the PTK2-phosphorylation at tyrosine 397 (pY397).

PC-3 cells (prostate carcinoma, ATCC CRL-1435) are grown in cell culture flasks (175 cm^2) with F12 Kaighn's Medium (Gibco, No.: 21127) with the addition of 10 % foetal calf serum (Invitrogen, No.: 16000-044). The cultures are incubated in the incubator at 37°C and 5 % CO_2 and run twice a week.

For the test, 2 x 10^4 cells pro well/180µL medium are plated out in 96-well microtitre plates (Costar, No.: 3598) and incubated overnight in the incubator at 37°C and 5 % CO_2. The test compounds (20 µL from serial dilution) are added the next day. The concentration of the test compounds usually covers a range of 10 µM and 5 fM. The test compounds (stock solution: 10 mM in 100 % DMSO) are first serially diluted in 100% DMSO and then diluted in medium such that the final concentration is 0.5 % DMSO. The cells are then incubated in the incubator at 37°C and 5 % CO_2 for 2 h. Then the culture supernatant is removed and the cells are fixed with 100 µL 4 % formaldehyde in D-PBS for 20 min at RT. After the removal of the formaldehyde solution, the cells are washed once with 300 µl of washing buffer (0.1 % Triton X-100 in D-PBS) for 5 min. Then they are incubated for 20 minutes in 100 µl per well of quenching solution (hydrogen peroxide 30%, sodium azide 10% in washing buffer) at RT. The cell lawn is again washed once with 300 µl washing buffer for 5 min and then for 1 hour with 100 µl per well of blocking buffer (5 % skimmed milk powder (Maresi Fixmilch) in TBST (25 mM Tris/HCl, pH 8.0, 150 mM NaCl, 0.05 % Tween 20). The blocking buffer is replaced by 50 µL of the first antibody anti-phospho PTK2 [pY397] rabbit monoclonal (Invitrogen/Biosource, No.: 44-625G), which is diluted 1:1000 in blocking buffer. For control purposes, alternatively a PTK2 [total] antibody (clone 4.47 mouse monoclonal, Upstate, No.: 05-537), diluted 1:400 in blocking buffer is used. This incubation is carried out at 4°C overnight. Then the cell lawn is washed once with 300 µL of washing buffer for 5 min and 50 µL/well of second antibody are added. In order to detect bound phospho-PTK2 [pY397] antibody a goat-anti-rabbit antibody is used which is coupled with horseradish peroxidase (Dako, No.: P0448; 1:500 dilution in blocking buffer). In order to detect bound PTK2 [total]-antibodies a rabbit-anti-mouse antibody is used, which is also coupled with horseradish peroxidase (Dako, No.: PO161; 1:1000 dilution in blocking buffer). This incubation is carried out for 1 h at RT with gentle shaking. The cell lawn is then again washed once with 300 µL of washing buffer for 5 min and then with 300 µl of PBS. The PBS is removed by suction filtering and peroxidase staining is carried out by adding 100 µL staining solution (1:1 mixture of TMB peroxidase substrate (KPL, No.: 50-76-02) and peroxidase solution B (H_2O_2) (KPL, No.: 50-65-02). The development of the stain takes place for 10 - 30 min in the dark. The reaction is stopped by the addition of 100 µL/well of a 1 M phosphoric acid solution. The absorption is determined photometrically at 450 nm with an absorption measuring device (VICTOR^3 PerkinElmer). The inhibition of the anti-phospho PTK2 [pY397] immune staining is used

to determine EC_{50} values. The staining with anti-PTK2 [total]-antibodies is for control purposes and should remain constant under the influence of inhibitor. The EC_{50} values are determined from concentration-activity analyses by iterative calculation with the aid of a sigmoid curve analysis algorithm (FIFTY, based on GraphPAD Prism Version 3.03) with a variable Hill coefficient.

All the Examples tested have an EC_{50} value (PC-3) of less than 10 µM, generally less than 1 µM.

The substances of the present invention are PTK2-kinase inhibitors. In view of their biological properties the new compounds of general formula **(1)**, the isomers thereof and the physiologically acceptable salts thereof are suitable for the treatment of diseases characterised by excessive or abnormal cell proliferation.

Such diseases include for example: viral infections (e.g. HIV and Kaposi's sarcoma); inflammatory and autoimmune diseases (e.g. colitis, arthritis, Alzheimer's disease, glomerulonephritis and wound healing); bacterial, fungal and/or parasitic infections; leukaemias, lymphomas and solid tumours (e.g. carcinomas and sarcomas), skin diseases (e.g. psoriasis); diseases based on hyperplasia which are characterised by an increase in the number of cells (e.g. fibroblasts, hepatocytes, bones and bone marrow cells, cartilage or smooth muscle cells or epithelial cells (e.g. endometrial hyperplasia)); bone diseases and cardiovascular diseases (e.g. restenosis and hypertrophy).

For example, the following cancers may be treated with compounds according to the invention, without being restricted thereto:
brain tumours such as for example acoustic neurinoma, astrocytomas such as fibrillary, protoplasmic, gemistocytary, anaplastic, pilocytic astrocytomas, glioblastoma, gliosarcoma, pleomorphic xanthoastrocytoma, subependymal large-cell giant cell astrocytoma and desmoplastic infantile astrocytoma; brain lymphomas, brain metastases, hypophyseal tumour such as prolactinoma, hypophyseal incidentaloma, HGH (human growth hormone) producing adenoma and corticotrophic adenoma, craniopharyngiomas, medulloblastoma, meningeoma and oligodendroglioma; nerve tumours such as for example tumours of the vegetative nervous system such as neuroblastoma, ganglioneuroma, paraganglioma (pheochromocytoma, chromaffinoma) and glomus-

caroticum tumour, tumours on the peripheral nervous system such as amputation neuroma, neurofibroma, neurinoma (neurilemmoma, Schwannoma) and malignant Schwannoma, as well as tumours of the central nervous system such as brain and bone marrow tumours; intestinal cancer such as for example carcinoma of the rectum, colon, anus and duodenum; eyelid tumours (basalioma or adenocarcinoma of the eyelid apparatus); retinoblastoma; carcinoma of the pancreas; carcinoma of the bladder; lung tumours (bronchial carcinoma - small-cell lung cancer (SCLC), non-small-cell lung cancer (NSCLC) such as for example spindle-cell plate epithelial carcinomas, adenocarcinomas (acinary, paillary, bronchiolo-alveolar) and large-cell bronchial carcinoma (giant cell carcinoma, clear-cell carcinoma)); breast cancer such as ductal, lobular, mucinous or tubular carcinoma, Paget's carcinoma; non-Hodgkin's lymphomas (B-lymphatic or T-lymphatic NHL) such as for example hair cell leukaemia, Burkitt's lymphoma or mucosis fungoides; Hodgkin's disease; uterine cancer (corpus carcinoma or endometrial carcinoma); CUP syndrome (Cancer of Unknown Primary); ovarian cancer (ovarian carcinoma - mucinous or serous cystoma, endometriodal tumours, clear cell tumour, Brenner's tumour); gall bladder cancer; bile duct cancer such as for example Klatskin tumour; testicular cancer (germinal or non-germinal germ cell tumours); laryngeal cancer such as for example supra-glottal, glottal and subglottal tumours of the vocal cords; bone cancer such as for example osteochondroma, chondroma, chondroblastoma, chondromyxoid fibroma, chondrosarcoma, osteoma, osteoid osteoma, osteoblastoma, osteosarcoma, non-ossifying bone fibroma, osteofibroma, desmoplastic bone fibroma, bone fibrosarcoma, malignant fibrous histiocyoma, osteoclastoma or giant cell tumour, Ewing's sarcoma, and plasmocytoma, head and neck tumours (HNO tumours) such as for example tumours of the lips, and oral cavity (carcinoma of the lips, tongue, oral cavity), nasopharyngeal carcinoma (tumours of the nose, lymphoepithelioma), pharyngeal carcinoma, oropharyngeal carcinomas, carcinomas of the tonsils (tonsil malignoma) and (base of the) tongue, hypopharyngeal carcinoma, laryngeal carcinoma (cancer of the larynx), tumours of the paranasal sinuses and nasal cavity, tumours of the salivary glands and ears; liver cell carcinoma (hepatocellular carcinoma (HCC); leukaemias, such as for example acute leukaemias such as acute lymphatic/lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML); chronic lymphatic leukaemia (CLL), chronic myeloid leukaemia (CML); stomach cancer (papillary, tubular or mucinous adenocarcinoma, adenosquamous, squamous or undifferentiated carcinoma; malignant melanomas such as for example superficially spreading (SSM), nodular (NMM), lentigo-maligna (LMM), acral-

lentiginous (ALM) or amelanotic melanoma (AMM); renal cancer such as for example kidney cell carcinoma (hypernephroma or Grawitz's tumour); oesophageal cancer; penile cancer; prostate cancer; vaginal tumors (vaginal carcinoma or cervical carcinoma); thyroid carcinomas such as for example papillary, follicular, medullary or anaplastic thyroid carcinoma; thymus carcinoma (thymoma); cancer of the urethra (carcinoma of the urethra, urothelial carcinoma) and vulvar carcinoma.

The new compounds may be used for the prevention, short-term or long-term treatment of the above-mentioned diseases, optionally also in combination with radiotherapy or other "state-of-the-art" compounds, such as e.g. cytostatic or cytotoxic substances, cell proliferation inhibitors, anti-angiogenic substances, steroids or antibodies.

The compounds of general formula (1) may be used on their own or in combination with other active substances according to the invention, optionally also in combination with other pharmacologically active substances.

Chemotherapeutic agents which may be administered in combination with the compounds according to the invention include, without being restricted thereto, hormones, hormone analogues and antihormones (e.g. tamoxifen, toremifene, raloxifene, fulvestrant, megestrol acetate, flutamide, nilutamide, bicalutamide, aminoglutethimide, cyproterone acetate, finasteride, buserelin acetate, fludrocortisone, fluoxymesterone, medroxyprogesterone, octreotide), aromatase inhibitors (e.g. anastrozole, letrozole, liarozole, vorozole, exemestane, atamestane), LHRH agonists and antagonists (e.g. goserelin acetate, luprolide), inhibitors of growth factors (growth factors such as for example "platelet derived growth factor" and "hepatocyte growth factor", inhibitors are for example "growth factor" antibodies, "growth factor receptor" antibodies and tyrosinekinase inhibitors, such as for example gefitinib, lapatinib and trastuzumab); signal transduction inhibitors (e.g. Imatinib and sorafenib); antimetabolites (e.g. antifolates such as methotrexate, premetrexed and raltitrexed, pyrimidine analogues such as 5-fluorouracil, capecitabin and gemcitabin, purine and adenosine analogues such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine, fludarabine); antitumour antibiotics (e.g. anthracyclins such as doxorubicin, daunorubicin, epirubicin and idarubicin, mitomycin-C, bleomycin, dactinomycin, plicamycin, streptozocin); platinum derivatives (e.g. cisplatin, oxaliplatin, carboplatin); alkylation agents (e.g. estramustin,

meclorethamine, melphalan, chlorambucil, busulphan, dacarbazin, cyclophosphamide, ifosfamide, temozolomide, nitrosoureas such as for example carmustin and lomustin, thiotepa); antimitotic agents (e.g. Vinca alkaloids such as for example vinblastine, vindesin, vinorelbin and vincristine; and taxanes such as paclitaxel, docetaxel); topoisomerase inhibitors (e.g. epipodophyllotoxins such as for example etoposide and etopophos, teniposide, amsacrin, topotecan, irinotecan, mitoxantron) and various chemotherapeutic agents such as amifostin, anagrelid, clodronat, filgrastin, interferon alpha, leucovorin, rituximab, procarbazine, levamisole, mesna, mitotane, pamidronate and porfimer.

Suitable preparations include for example tablets, capsules, suppositories, solutions, - particularly solutions for injection (s.c., i.v., i.m.) and infusion - syrups, elixirs, emulsions or dispersible powders. The content of the pharmaceutically active compound(s) should be in the range from 0.1 to 90 wt.-%, preferably 0.5 to 50 wt.-% of the composition as a whole, i.e. In amounts which are sufficient to achieve the dosage range specified below. The doses specified may, if necessary, be given several times a day.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange

extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose) emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

The preparations are administered by the usual methods, preferably by oral or transdermal route, most preferably by oral route. For oral administration the tablets may, of course contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tabletting process. In the case of aqueous suspensions the active substances may be

combined with various flavour enhancers or colourings in addition to the excipients mentioned above.
For parenteral use, solutions of the active substances with suitable liquid carriers may be used.

The dosage for intravenous use is from 1 - 1000 mg per hour, preferably between 5 and 500 mg per hour.

However, it may sometimes be necessary to depart from the amounts specified, depending on the body weight, the route of administration, the individual response to the drug, the nature of its formulation and the time or interval over which the drug is administered. Thus, in some cases it may be sufficient to use less than the minimum dose given above, whereas in other cases the upper limit may have to be exceeded. When administering large amounts it may be advisable to divide them up into a number of smaller doses spread over the day.

The formulation examples that follow illustrate the present invention without restricting its scope:

Examples of pharmaceutical formulations

A) Tablets per tablet

active substance according to formula **(1)**	100 mg
lactose	140 mg
corn starch	240 mg
polyvinylpyrrolidone	15 mg
magnesium stearate	5 mg
	500 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B) Tablets per tablet

active substance according to formula **(1)**	80 mg
lactose	55 mg
corn starch	190 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone	15 mg
sodium-carboxymethyl starch	23 mg
magnesium stearate	2 mg
	400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened.

The sodiumcarboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

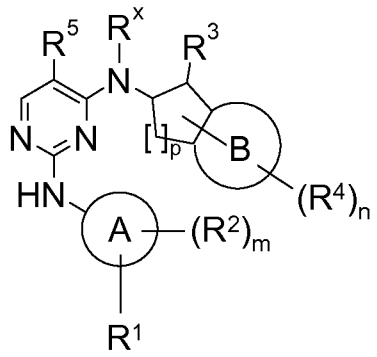
C) Ampoule solution

active substance according to formula **(1)**	50 mg
sodium chloride	50 mg
water for inj.	5 ml

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

Claims

1. Compounds of general formula **(1)**



(1) , wherein

A is a group selected from among C_{6-15}aryl and 5-12 membered heteroaryl;

B is a group selected from among C_{6-10}aryl and 5-10 membered heteroaryl;

$\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^4}$ and $\mathbf{R^x}$ in each case independently of one another denote hydrogen or a group selected from among $\mathbf{R^a}$, $\mathbf{R^b}$ and $\mathbf{R^a}$ substituted by one or more, identical or different $\mathbf{R^c}$ and/or $\mathbf{R^b}$;

$\mathbf{R^3}$ is a group selected from among $-NR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, $-N(R^g)C(O)R^c$, $-N[C(O)R^c]_2$, $-N(OR^g)C(O)R^c$, $-N(R^g)C(NR^g)R^c$, $-N(R^g)N(R^g)C(O)R^c$, $-N[C(O)R^c]NR^cR^c$, $-N(R^g)C(S)R^c$, $-N(R^g)S(O)R^c$, $-N(R^g)S(O)OR^c$, $-N(R^g)S(O)_2R^c$, $-N[S(O)_2R^c]_2$, $-N(R^g)S(O)_2OR^c$, $-N(R^g)S(O)_2NR^cR^c$, $-N(R^g)[S(O)_2]_2R^c$, $-N(R^g)C(O)OR^c$, $-N(R^g)C(O)SR^c$, $-N(R^g)C(O)NR^cR^c$, $-N(R^g)C(O)NR^gNR^cR^c$, $-N(R^g)N(R^g)C(O)NR^cR^c$, $-N(R^g)C(S)NR^cR^c$, $-[N(R^g)C(O)]_2R^c$, $-N(R^g)[C(O)]_2R^c$, $-N\{[C(O)]_2R^c\}_2$, $-N(R^g)[C(O)]_2OR^c$, $-N(R^g)[C(O)]_2NR^cR^c$, $-N\{[C(O)]_2OR^c\}_2$, $-N\{[C(O)]_2NR^cR^c\}_2$, $-[N(R^g)C(O)]_2OR^c$, $-N(R^g)C(NR^g)OR^c$, $-N(R^g)C(NOH)R^c$, $-N(R^g)C(NR^g)SR^c$ and $-N(R^g)C(NR^g)NR^cR^c$;

$\mathbf{R^5}$ is a group selected from among halogen, -CN, $-NO_2$, $-OR^c$, $-C(O)R^c$, $-NR^cR^c$, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl and 3-8 membered heterocycloalkyl;

each $\mathbf{R^a}$ is independently selected from among C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^b** is a suitable group and is independently selected from among =O, -OR^c, C_{1-3}haloalkyloxy, -OCF$_3$, =S, -SR^c, =NR^c, =NOR^c, =NNR^{c}R^c, =NN(R^g)C(O)NR^{c}R^c, -NR^{c}R^c, -ONR^{c}R^c, -N(OR^c)R^c, -N(R^g)NR^{c}R^c, halogen, -CF$_3$, -CN, -NC, -OCN, -SCN, -NO, -NO$_2$, =N$_2$, -N$_3$, -S(O)R^c, -S(O)OR^c, -S(O)$_2$R^c, -S(O)$_2$OR^c, -S(O)NR^{c}R^c, -S(O)$_2$NR^{c}R^c, -OS(O)R^c, -OS(O)$_2$R^c, -OS(O)$_2$OR^c, -OS(O)NR^{c}R^c, -OS(O)$_2$NR^{c}R^c, -C(O)R^c, -C(O)OR^c, -C(O)SR^c, -C(O)NR^{c}R^c, -C(O)N(R^g)NR^{c}R^c, -C(O)N(R^g)OR^c, -C(NR^g)NR^{c}R^c, -C(NOH)R^c, -C(NOH)NR^{c}R^c, -OC(O)R^c, -OC(O)OR^c, -OC(O)SR^c, -OC(O)NR^{c}R^c, -OC(NR^g)NR^{c}R^c, -SC(O)R^c, -SC(O)OR^c, -SC(O)NR^{c}R^c, -SC(NR^g)NR^{c}R^c, -N(R^g)C(O)R^c, -N[C(O)R^c]$_2$, -N(OR^g)C(O)R^c, -N(R^g)C(NR^g)R^c, -N(R^g)N(R^g)C(O)R^c, -N[C(O)R^c]NR^{c}R^c, -N(R^g)C(S)R^c, -N(R^g)S(O)R^c, -N(R^g)S(O)OR^c, -N(R^g)S(O)$_2$R^c, -N[S(O)$_2$R^c]$_2$, -N(R^g)S(O)$_2$OR^c, -N(R^g)S(O)$_2$NR^{c}R^c, -N(R^g)[S(O)$_2$]$_2$R^c, -N(R^g)C(O)OR^c, -N(R^g)C(O)SR^c, -N(R^g)C(O)NR^{c}R^c, -N(R^g)C(O)NR^{g}NR^{c}R^c, -N(R^g)N(R^g)C(O)NR^{c}R^c, -N(R^g)C(S)NR^{c}R^c, -[N(R^g)C(O)]$_2$R^c, -N(R^g)[C(O)]$_2$R^c, -N{[C(O)]$_2$R^c}$_2$, -N(R^g)[C(O)]$_2$OR^c, -N(R^g)[C(O)]$_2$NR^{c}R^c, -N{[C(O)]$_2$OR^c}$_2$, -N{[C(O)]$_2$NR^{c}R^c}$_2$, -[N(R^g)C(O)]$_2$OR^c, -N(R^g)C(NR^g)OR^c, -N(R^g)C(NOH)R^c, -N(R^g)C(NR^g)SR^c and -N(R^g)C(NR^g)NR^{c}R^c;

each **R^c** independently denotes hydrogen or a group optionally substituted by one or more, identical or different **R^d** and/or **R^e**, selected from among C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{4-11}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^d** denotes a suitable group and is independently selected from among =O, -OR^e, C_{1-3}haloalkyloxy, -OCF$_3$, =S, -SR^e, =NR^e, =NOR^e, =NNR^{e}R^e, =NN(R^g)C(O)NR^{e}R^e, -NR^{e}R^e, -ONR^{e}R^e, -N(R^g)NR^{e}R^e, halogen, -CF$_3$, -CN, -NC, -OCN, -SCN, -NO, -NO$_2$, =N$_2$, -N$_3$, -S(O)R^e, -S(O)OR^e, -S(O)$_2$R^e, -S(O)$_2$OR^e, -S(O)NR^{e}R^e, -S(O)$_2$NR^{e}R^e, -OS(O)R^e, -OS(O)$_2$R^e, -OS(O)$_2$OR^e, -OS(O)NR^{e}R^e, -OS(O)$_2$NR^{e}R^e, -C(O)R^e, -C(O)OR^e, -C(O)SR^e, -C(O)NR^{e}R^e, -C(O)N(R^g)NR^{e}R^e, -C(O)N(R^g)OR^e, -C(NR^g)NR^{e}R^e, -C(NOH)R^e, -C(NOH)NR^{e}R^e, -OC(O)R^e, -OC(O)OR^e, -OC(O)SR^e, -OC(O)NR^{e}R^e, -OC(NR^g)NR^{e}R^e, -SC(O)R^e, -SC(O)OR^e, -SC(O)NR^{e}R^e, -SC(NR^g)NR^{e}R^e, -N(R^g)C(O)R^e, -N[C(O)R^e]$_2$, -N(OR^g)C(O)R^e, -N(R^g)C(NR^g)R^e, -N(R^g)N(R^g)C(O)R^e, -N[C(O)R^e]NR^{e}R^e, -N(R^g)C(S)R^e, -N(R^g)S(O)R^e, -N(R^g)S(O)OR^e, -N(R^g)S(O)$_2$R^e, -N[S(O)$_2$R^e]$_2$, -N(R^g)S(O)$_2$OR^e, -N(R^g)S(O)$_2$NR^{e}R^e, -N(R^g)[S(O)$_2$]$_2$R^e, -N(R^g)C(O)OR^e, -N(R^g)C(O)SR^e, -N(R^g)C(O)NR^{e}R^e, -N(R^g)C(O)NR^{g}NR^{e}R^e, -N(R^g)N(R^g)C(O)NR^{e}R^e, -N(R^g)C(S)NR^{e}R^e, -[N(R^g)C(O)]$_2$R^e, -N(R^g)[C(O)]$_2$R^e, -N{[C(O)]$_2$R^e}$_2$, -N(R^g)[C(O)]$_2$OR^e, -N(R^g)[C(O)]$_2$NR^{e}R^e, -N{[C(O)]$_2$OR^e}$_2$,

$-N\{[C(O)]_2NR^eR^e\}_2$, $-[N(R^g)C(O)]_2OR^e$, $-N(R^g)C(NR^g)OR^e$, $-N(R^g)C(NOH)R^e$, $-N(R^g)C(NR^g)SR^e$ and $-N(R^g)C(NR^g)NR^eR^e$;

each **R^e** independently denotes hydrogen or a group optionally substituted by one or more, identical or different **R^f** and/or **R^g**, selected from among C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{4-11}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^f** denotes a suitable group and is independently selected from among halogen, $-OR^g$ and $-CF_3$;

each **R^g** independently denotes hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{4-11}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkyl, 5-12 membered heteroaryl or 6-18 membered heteroarylalkyl and

m is equal to 1, 2 or 3;

n is equal to 0, 1, 2, 3 or 4;

p is equal to 0, 1, 2 or 3;

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

2. Compounds according to claim 1, wherein

R^x is hydrogen.

3. Compounds according to claim 1 or 2, wherein

B is phenyl or 5-6 membered heteroaryl and

R^4 and **n** are defined as in claim 1.

4. Compounds according to claim 3, wherein

n has the value 0.

5. Compounds according to one of claims 1 to 4, wherein

$\mathbf{R^5}$ is a group selected from among halogen, $-CF_3$ and C_{1-4}haloalkyl.

6. Compounds according to one of claims 1 to 5, wherein

$\mathbf{R^3}$ is selected from among $-NR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, $-N(R^g)C(O)R^c$, $-N(OR^g)C(O)R^c$, $-N(R^g)N(R^g)C(O)R^c$, $-N(R^g)S(O)_2R^c$, $-N(R^g)C(O)OR^c$ and $-N(R^g)C(O)NR^cR^c$, and

$\mathbf{R^c}$ and $\mathbf{R^g}$ are defined as in claim 1.

7. Compounds according to claim 6, wherein

$\mathbf{R^3}$ is selected from among $-N(R^g)C(O)R^c$, $-N(R^g)C(O)OR^c$ and $-N(R^g)S(O)_2R^c$, and

$\mathbf{R^c}$ and $\mathbf{R^g}$ are defined as in claim 1.

8. Compounds according to one of claims 1 to 7, wherein

A is a group selected from among phenyl and 5-10 membered heteroaryl and

$\mathbf{R^1}$, $\mathbf{R^2}$ and **m** are defined as in claim 1.

9. Compounds according to claim 8, wherein

A is a phenyl;

m has the value 1 or 2;

each $\mathbf{R^2}$ is independently selected from among halogen, C_{1-6}alkyl and C_{1-6}alkoxy and

$\mathbf{R^1}$ is defined as in claim 1.

10. Compounds according to one of claims 8 or 9, wherein

$\mathbf{R^1}$ is selected from among $\mathbf{R^{a2}}$, $\mathbf{R^{b2}}$ and $\mathbf{R^{a2}}$ substituted by one or more, identical or different $\mathbf{R^{b2}}$ and/or $\mathbf{R^{c2}}$;

each $\mathbf{R^{a2}}$ is independently selected from among C_{1-6}alkyl and 3-7 membered heterocycloalkyl;

each $\mathbf{R^{b2}}$ denotes a suitable substituent and is independently selected from among O=, $-OR^{c2}$, $-NR^{c2}R^{c2}$, $-C(O)R^{c2}$, $-C(O)OR^{c2}$, $-C(O)NR^{c2}R^{c2}$, $-C(O)N(R^{g2})OR^{c2}$, $-N(R^{g2})C(O)R^{c2}$, $-N(R^{g2})C(O)OR^{c2}$ and $-N(R^{g2})C(O)NR^{c2}R^{c2}$,

each $\mathbf{R^{c2}}$ independently denotes hydrogen or a group optionally substituted by one or more, identical or different $\mathbf{R^{d2}}$ and/or $\mathbf{R^{e2}}$, selected from among C_{1-6}alkyl, C_{3-6}cycloalkyl and 3-7 membered heterocycloalkyl;

each $\mathbf{R^{d2}}$ denotes a suitable substituent and is independently selected from among $-OR^{e2}$, $-NR^{e2}R^{e2}$ and $-C(O)N(R^{g2})OR^{e2}$,$-C(O)NR^{e2}R^{e2}$;

each $\mathbf{R^{e2}}$ independently denotes hydrogen or a group optionally substituted by one or more, identical or different $\mathbf{R^{f2}}$ and/or $\mathbf{R^{g2}}$, selected from among C_{1-6}alkyl, C_{3-6}cycloalkyl and 3-7 membered heterocycloalkyl;

each $\mathbf{R^{f2}}$ independently denotes $-OR^{g2}$ and

each $\mathbf{R^{g2}}$ is independently selected from among hydrogen, C_{1-6}alkyl and C_{4-9}cycloalkylalkyl.

11. Compounds according to claim 1 selected from among

I-3 *N*-(2-dimethylamino-ethyl)-4-[4-((1*R*,2*R*)-1-methanesulphonylamino-indan-2-ylamino)-5-trifluoromethyl-pyrimidin-2-ylamino]-3-methoxy-benzamide;

I-5 4-{4-[(1 *R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-39 *N*-((1 *R*,2*R*)-2-{2-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-5-trifluoromethyl-pyrimidin-4-ylamino}-indan-1-yl)-*N*-methyl-methanesulphonamide;

I-40 2-[4-(4-{4-[(1 *R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-phenyl)-piperazin-1-yl]-*N*,*N*-dimethyl-acetamide;

I-46 2-fluoro-4-{4-[(1 *R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-60 2-chloro-4-{4-[(1 *R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-61 1-methyl-pyrrolidine-3-carboxylic acid (3-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-4-methoxy-phenyl)-amide;

I-62 1-methyl-piperidine-4-carboxylic acid (3-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-4-methoxy-phenyl)-amide;

I-63 *N*-(2-dimethylamino-ethyl)-3-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-4-methoxy-benzamide;

I-66 *N*-((1*R*,2*R*)-2-{2-[4-(4-*tert*-butyl-piperazin-1-yl)-2-methoxy-phenylamino]-5-trifluoromethyl-pyrimidin-4-ylamino}-indan-1-yl)-*N*-methyl-methanesulphonamide;

I-67 *N*-((1*R*,2*R*)-2-{2-[5-ethyl-2-methoxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-5-trifluoromethyl-pyrimidin-4-ylamino}-indan-1-yl)-*N*-methyl-methanesulphonamide;

I-70 *N*-{(1*R*,2*R*)-2-[2-(2-methoxy-4-piperazin-1-yl-phenylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-indan-1-yl}-*N*-methyl-methanesulphonamide;

I-74 *N*-{(1*R*,2*R*)-2-[2-(2-methoxy-5-methyl-4-piperazin-1-yl-phenylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-indan-1-yl}-*N*-methyl-methanesulphonamide;

I-75 5-{5-chloro-4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-pyrimidin-2-ylamino}-2-fluoro-4-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-76 *N*-{(1*R*,2*R*)-2-[2-(5-chloro-2-methoxy-4-piperazin-1-yl-phenylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-indan-1-yl}-*N*-methyl-methanesulphonamide;

I-78 *N*-((1*R*,2*R*)-2-{2-[4-(4-*tert*-butyl-piperazin-1-yl)-2-methoxy-5-methyl-phenylamino]-5-trifluoromethyl-pyrimidin-4-ylamino}-indan-1-yl)-*N*-methyl-methanesulphonamide;

I-80 2-fluoro-5-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-4-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-98 4-{5-bromo-4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-pyrimidin-2-ylamino}-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide;

I-73 1-methyl-piperidine-4-carboxylic acid (4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-ylamino]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-phenyl)-amide and

I-71 *N*-{(1*R*,2*R*)-2-[2-(2-methoxy-4-methylaminomethyl-phenylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-indan-1-yl}-*N*-methyl-methanesulphonamide.

12. Compounds of general formula **(1)** according to one of claims 1 to 11 – or the pharmaceutically acceptable salts thereof – as medicaments.

13. Compounds of general formula **(1)** according to one of claims 1 to 11 – or the pharmaceutically acceptable salts thereof – for use in the treatment and/or prevention of cancer, infections, inflammations and autoimmune diseases.

14. Pharmaceutical preparation containing as active substance one or more compounds of general formula **(1)** according to one of claims 1 to 11 – or the pharmaceutically acceptable salts thereof – optionally in combination with conventional excipients and/or carriers.

15. Pharmaceutical preparation comprising a compound of general formula **(1)** according to one of claims 1 to 11 – or one of the pharmaceutically acceptable salts thereof – and at least one other cytostatic or cytotoxic active substance different from formula **(1)**.