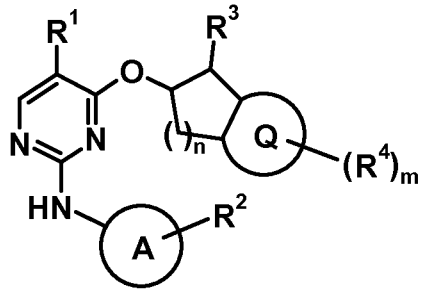
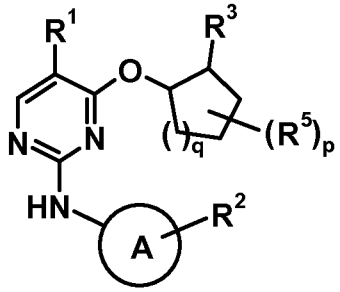
PYRIMIDINE DERIVATIVES AS PROTEIN TYROSINE KINASE 2 INHIBITORS

The present invention relates to new pyrimidines of general formulae **(1a)** and **(1b)**



(1a)



(1b)

,

wherein the groups R^1 to R^5, **A**, **Q**, **m**, **n**, **p** and **q** 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.

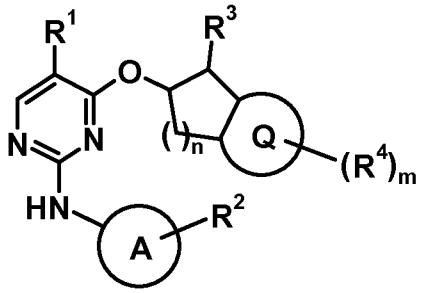
Pyrimidines are generally known as inhibitors of kinases. Thus, for example, pyrimidines are described as aurora-kinase inhibitors in International Patent Application WO 2008/038011, these pyridines having, as substituents, an oxymethylpiperidinyl group in the 4 position and fluorine in the 5 position.

The aim of the present invention is to indicate new pyrimidines 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 pyrimidines 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.

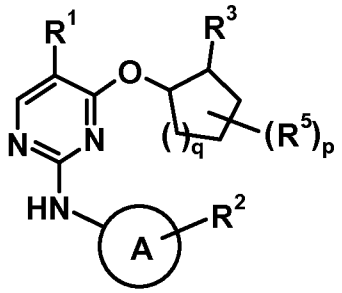
Detailed description of the invention

It has now been found that, surprisingly, compounds of general formulae **(1a)** and **(1b)**, wherein the groups $\mathbf{R^1}$ to $\mathbf{R^5}$, **A**, **Q**, **m**, **n**, **p** and **q** have the meanings given hereinafter act as inhibitors of specific tyrosine-kinases. Thus the compounds according to the invention may be used for example for the treatment of diseases connected to the activity of specific tyrosine-kinases and characterised by excessive or abnormal cell proliferation.

The present invention relates to compounds of general formulae **(1a)** and **(1b)**



(1a)



(1b)

,

wherein

A denotes a group, optionally substituted by one or more, identical or different $\mathbf{R^2}$, selected from among C_{3-10}cycloalkyl, 3-8 membered heterocycloalkyl, C_{6-15}aryl and 5-12 membered heteroaryl;

Q denotes a group, optionally substituted by one or more, identical or different $\mathbf{R^4}$, selected from among phenyl and 5-6 membered heteroaryl;

$\mathbf{R^1}$ denotes a group selected from among halogen, $-OR^c$, $-OCF_3$, $-SR^c$, $-NR^cR^c$, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, C_{1-3}alkyl, C_{1-3}haloalkyl and C_{1-3}haloalkyloxy;

$\mathbf{R^2}$, $\mathbf{R^4}$ and $\mathbf{R^5}$ 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 $\mathbf{R^b}$;

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

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 $\mathbf{R^b}$ is a suitable group and each is independently selected from among =O, $-OR^c$, $C_{1\text{-}3}$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 $C_{1\text{-}6}$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** is a suitable group and each is independently selected from among =O, $-OR^e$, C_{1-3}haloalkyloxy, $-OCF_3$, =S, $-SR^e$, $=NR^e$, $=NOR^e$, $=NNR^eR^e$, $=NN(R^g)C(O)NR^eR^e$, $-NR^eR^e$, $-ONR^eR^e$, $-N(R^g)NR^eR^e$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^e$, $-S(O)OR^e$, $-S(O)_2R^e$, $-S(O)_2OR^e$, $-S(O)NR^eR^e$, $-S(O)_2NR^eR^e$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)_2OR^e$, $-OS(O)NR^eR^e$, $-OS(O)_2NR^eR^e$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)SR^e$, $-C(O)NR^eR^e$, $-C(O)N(R^g)NR^eR^e$, $-C(O)N(R^g)OR^e$, $-C(NR^g)NR^eR^e$, $-C(NOH)R^e$, $-C(NOH)NR^eR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)SR^e$, $-OC(O)NR^eR^e$, $-OC(NR^g)NR^eR^e$, $-SC(O)R^e$, $-SC(O)OR^e$, $-SC(O)NR^eR^e$, $-SC(NR^g)NR^eR^e$, $-N(R^g)C(O)R^e$, $-N[C(O)R^e]_2$, $-N(OR^g)C(O)R^e$, $-N(R^g)C(NR^g)R^e$, $-N(R^g)N(R^g)C(O)R^e$, $-N[C(O)R^e]NR^eR^e$, $-N(R^g)C(S)R^e$, $-N(R^g)S(O)R^e$, $-N(R^g)S(O)OR^e$, $-N(R^g)S(O)_2R^e$, $-N[S(O)_2R^e]_2$, $-N(R^g)S(O)_2OR^e$, $-N(R^g)S(O)_2NR^eR^e$, $-N(R^g)[S(O)_2]_2R^e$, $-N(R^g)C(O)OR^e$, $-N(R^g)C(O)SR^e$, $-N(R^g)C(O)NR^eR^e$, $-N(R^g)C(O)NR^gNR^eR^e$, $-N(R^g)N(R^g)C(O)NR^eR^e$, $-N(R^g)C(S)NR^eR^e$, $-[N(R^g)C(O)]_2R^e$, $-N(R^g)[C(O)]_2R^e$, $-N\{[C(O)]_2R^e\}_2$, $-N(R^g)[C(O)]_2OR^e$, $-N(R^g)[C(O)]_2NR^eR^e$, $-N\{[C(O)]_2OR^e\}_2$, $-N\{[C(O)]_2NR^eR^e\}_2$, $-[N(R^g)C(O)]_2OR^e$, $-N(R^g)C(NR^g)OR^e$, $-N(R^g)C(NOH)R^e$, $-N(R^g)C(NR^g)SR^e$ 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** is a suitable group and each is independently selected from among halogen and $-CF_3$;

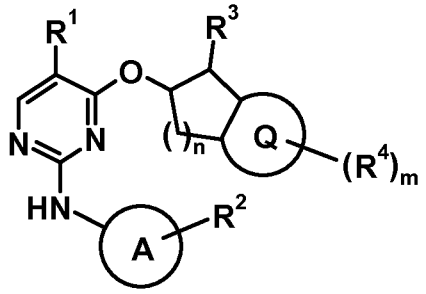
each **R^g** independently denotes hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{4-11}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkyl, 5-12 membered heteroaryl or 6-18 membered heteroarylalkyl;

m and **p** independently of one another denote 0, 1, 2 or 3 and

n and **q** denote 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 salts thereof, particularly the pharmacologically acceptable acid addition salts thereof.

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



(1a)

,

wherein

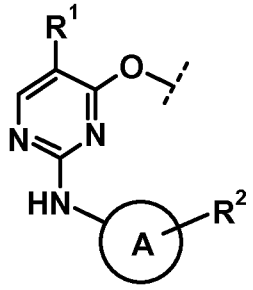
R^1, **R^2**, **R^3**, **R^4**, **A**, **Q**, **n** and **m** are as hereinbefore defined.

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

n is 1.

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

the group **R^3** and the group



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

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

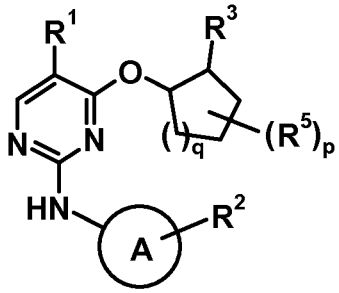
Q is phenyl and

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

In another preferred embodiment **(B2)** the present invention relates to compounds of general formula **(1a)**, wherein

m is 0.

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



(1b)

,

wherein

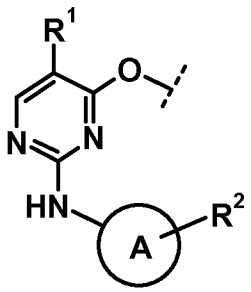
$\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^5}$, **A**, **p** and **q** are as hereinbefore defined.

In another preferred embodiment **(A3)** the present invention relates to compounds of general formula **(1b)**, wherein

q is equal to 1 or 2.

In another preferred embodiment **(A4)** the present invention relates to compounds of general formula **(1b)**, wherein

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



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

In another preferred embodiment **(B3)** the present invention relates to compounds of general formula **(1b)**, wherein

p is equal to 0.

In another preferred embodiment **(C1)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

$\mathbf{R^1}$ is a group selected from among halogen, $-CF_3$, -CN, $C_{1\text{-}3}$alkyl and $C_{1\text{-}3}$haloalkyl.

In another preferred embodiment **(C2)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

$\mathbf{R^1}$ is a group selected from among halogen and $-CF_3$.

In another preferred embodiment **(C3)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

$\mathbf{R^1}$ denotes $-CF_3$.

In another preferred embodiment **(C4)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

$\mathbf{R^1}$ denotes chlorine.

In another preferred embodiment **(D1)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

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

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

In another preferred embodiment **(D2)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

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

R^c and **R^g** are as hereinbefore defined.

In another preferred embodiment **(D3)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

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

R^c and **R^g** are as hereinbefore defined.

In another preferred embodiment **(D4)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

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

R^{c1} corresponds to the group **R^c** and

R^c and **R^g** are as hereinbefore defined.

In another preferred embodiment **(D5)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

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 $-N(C_{1\text{-}4}alkyl)S(O)_2R^{c1}$;

R^{c1} corresponds to the group **R^c** and

R^c is as hereinbefore defined.

In another preferred embodiment **(D6)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

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 $-N(n\text{Pr})S(O)_2R^{c1}$;

R^{c1} corresponds to the group **R^c** and

R^c is as hereinbefore defined.

In other preferred embodiments **(D7)(D8)(D9)** the present invention relates to compounds of the preferred embodiments **(D4)** and/or **(D5)** and/or **(D6)**, wherein

$\mathbf{R^{c1}}$ is selected from among C_{1-4}alkyl, C_{1-4}haloalkyl, 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 **(D10)(D11)(D12)** the present invention relates to compounds of the preferred embodiments **(D4)** and/or **(D5)** and/or **(D6)**, wherein

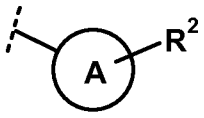
$\mathbf{R^{c1}}$ is selected from among methyl and ethyl.

In another preferred embodiment **(D13)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

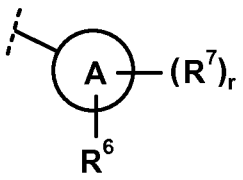
$\mathbf{R^3}$ denotes -N(Me)S(O)$_2$Me.

In another preferred embodiment **(E1)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

the group



denotes



,

$\mathbf{R^6}$ and $\mathbf{R^7}$ are defined as $\mathbf{R^2}$ hereinbefore,

r is equal to 1 or 2 and

A is as hereinbefore defined.

In another preferred embodiment **(E2)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

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

R^6, R^7 and **r** are as hereinbefore defined.

In another preferred embodiment **(E3)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

A is phenyl and

R^6, R^7 and **r** are as hereinbefore defined.

In another preferred embodiment **(E4)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

A is a phenyl;

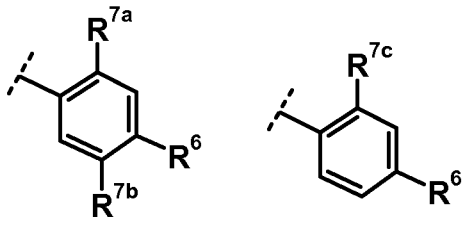
r has the value 1 or 2;

each R^7 is independently selected from among halogen, C_{1-6}alkyl and C_{1-6}alkoxy and

R^6 is as hereinbefore defined.

In another preferred embodiment **(E5)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

A together with R^6 and the **r** substituents R^7 has the partial structure



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

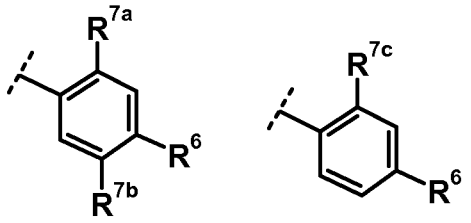
R^{7a} and R^{7c} each independently denote C_{1-6}alkoxy;

R^{7b} is selected from among halogen and C_{1-6}alkyl and

R^6 is as hereinbefore defined.

In another preferred embodiment **(E6)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

A together with R^6 and the **r** substituents R^7 has the partial structure



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

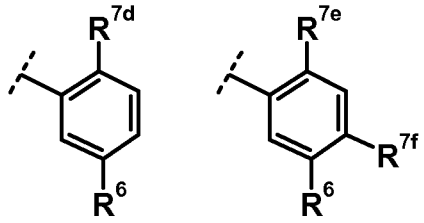
R^{7a} and R^{7c} each independently denote methoxy;

R^{7b} is selected from among fluorine, chlorine, methyl and ethyl and

R^6 is as hereinbefore defined.

In another preferred embodiment **(E7)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

A together with R^6 and the **r** substituents R^7 has the partial structure



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

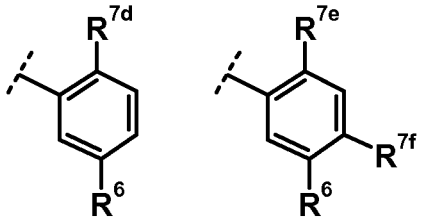
R^{7d} and R^{7e} each independently of one another denote C_{1-6}alkoxy;

R^{7f} is selected from among halogen and C_{1-6}alkyl and

R^6 is as hereinbefore defined.

In another preferred embodiment **(E8)** the present invention relates to compounds of general formulae **(1a)** and **(1b)**, wherein

A together with R^6 and the **r** substituents R^7 has the partial structure



(iii) or (iv) ;

R^{7d} and R^{7e} each independently denote methoxy;

R^{7f} is selected from among fluorine and methyl and

R^6 is as hereinbefore defined.

In other preferred embodiments **(E9)** the present invention relates to compounds of the preferred embodiments **(E1)** to **(E8)**, wherein

R^6 is selected from among hydrogen, R^{a2}, R^{b2} and R^{a2} substituted by one or more, identical or different R^{b2} and/or R^{c2};

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

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

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

each R^{e2} independently denotes hydrogen or a group optionally substituted by one or more, identical or different R^{f2} and/or R^{g2}, selected from among C_{1-6}alkyl, C_{3-6}cycloalkyl, 5-6 membered heteroaryl and 3-7 membered heterocycloalkyl;

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

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

In other preferred embodiments **(E10)** the present invention relates to compounds of the preferred embodiments **(E9)**, wherein

$\mathbf{R^6}$ denotes -C(O)NHR^{c2} or -C(O)N(Me)R^{c2} and

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

In other preferred embodiments **(E11)** the present invention relates to compounds of the preferred embodiments **(E9)**, wherein

$\mathbf{R^6}$ denotes -NHC(O)R^{c2} or -N(Me)C(O)R^{c2} and

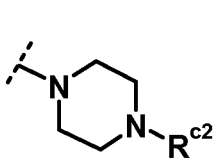
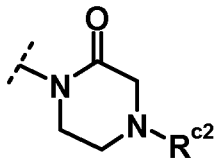
$\mathbf{R^{c2}}$ is as hereinbefore defined.

In other preferred embodiments **(E12)** the present invention relates to compounds of the preferred embodiments **(E9)** to **(E11)**, wherein

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

In other preferred embodiments **(E13)** the present invention relates to compounds of the preferred embodiments **(E9)**, wherein

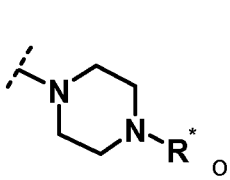
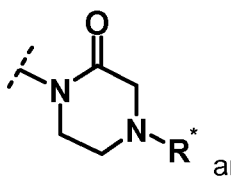
$\mathbf{R^6}$ denotes


or

and

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

In other preferred embodiments **(E14)** the present invention relates to compounds of the preferred embodiments **(E9)**, wherein

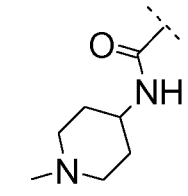
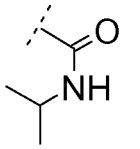
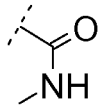
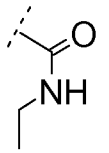
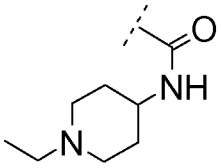
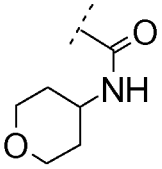
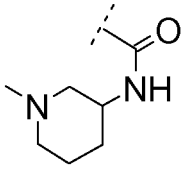
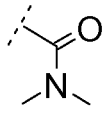
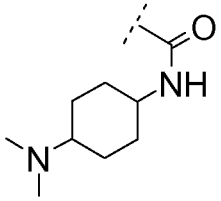
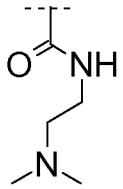
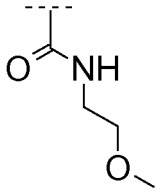
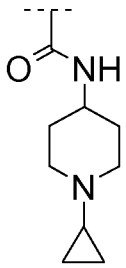
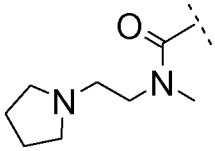
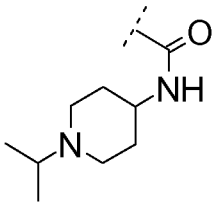
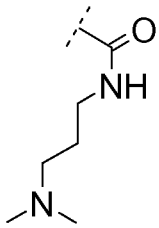
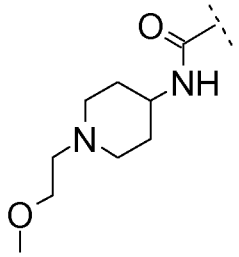
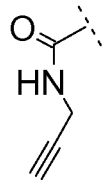
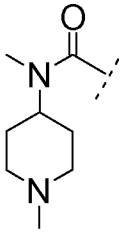
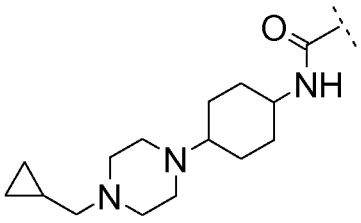
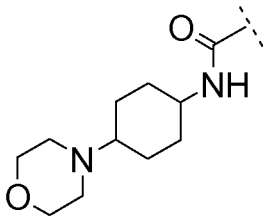
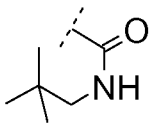
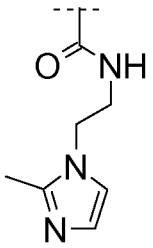
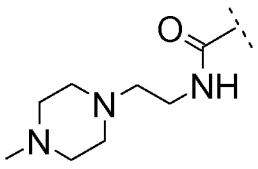
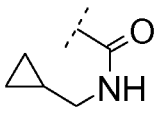
$\mathbf{R^6}$ denotes

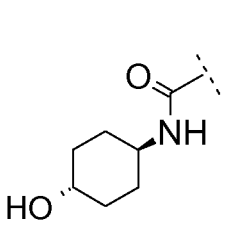
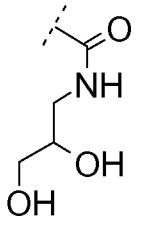
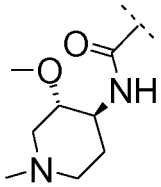
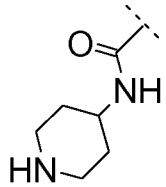
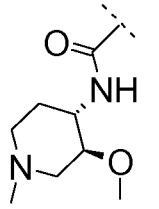
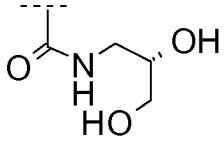
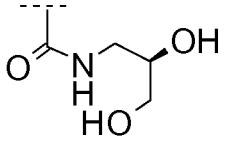

or

and

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

In other preferred embodiments **(E15)** the present invention relates to compounds of the preferred embodiments **(E9)**, wherein

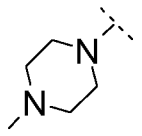
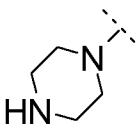
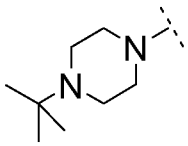
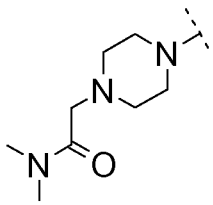
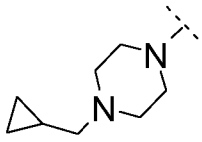
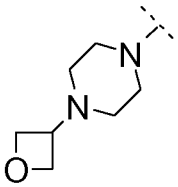
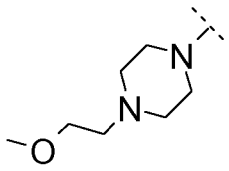
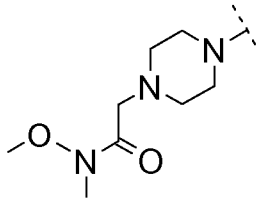
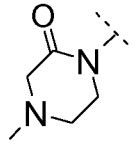
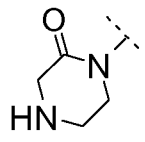
R^6 is selected from among


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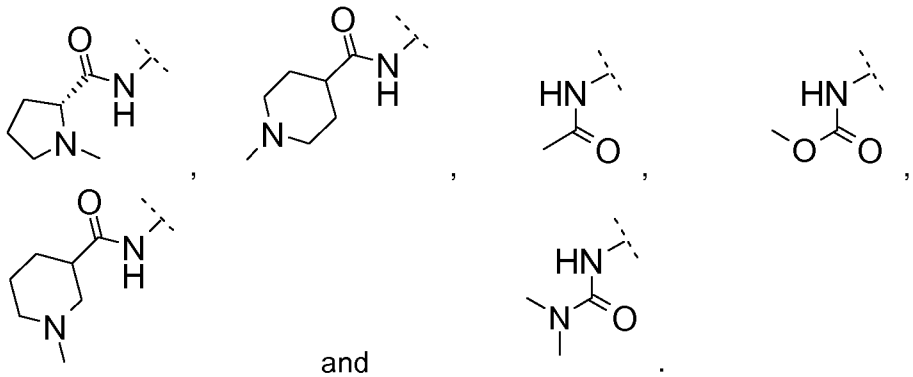
In other preferred embodiments **(E16)** the present invention relates to compounds of the preferred embodiments **(E9)**, wherein

R^{6} is selected from among


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In other preferred embodiments **(E17)** the present invention relates to compounds of the preferred embodiments **(E9)**, wherein

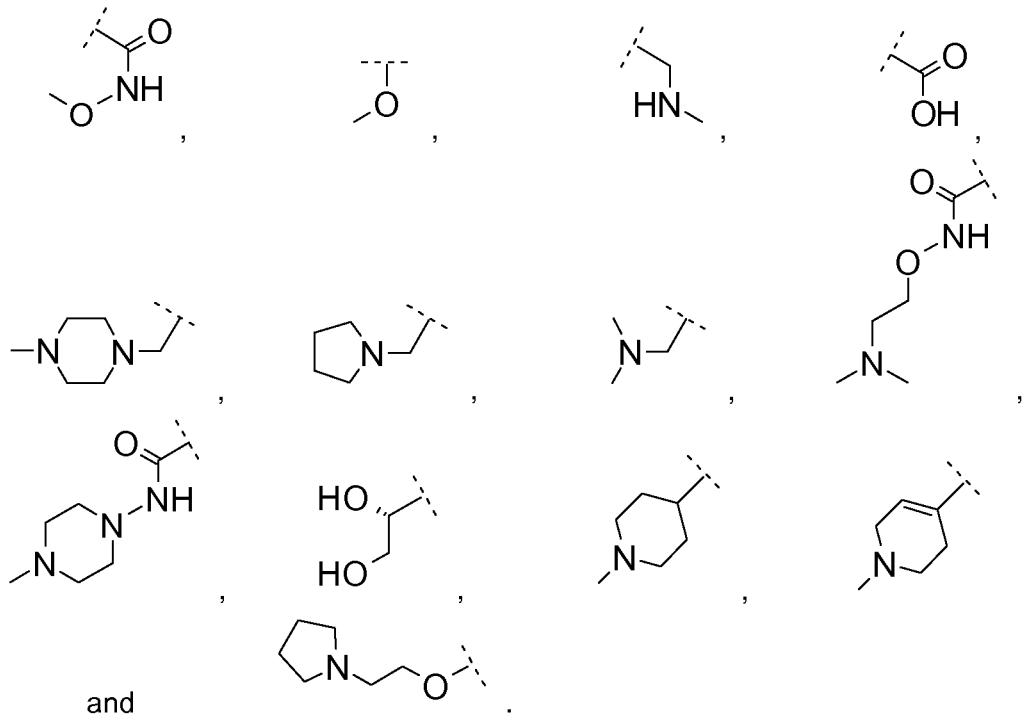
R^{6} is selected from among



and

In other preferred embodiments **(E18)** the present invention relates to compounds of the preferred embodiments **(E9)**, wherein

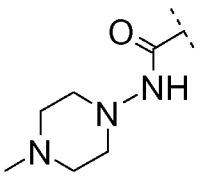
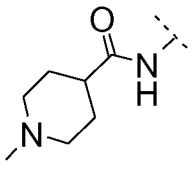
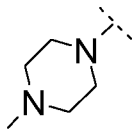
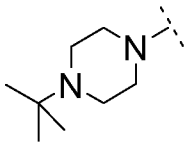
R^6 is selected from among



and

In other preferred embodiments **(E19)** the present invention relates to compounds of the preferred embodiments **(E9)**, wherein

R^6 is selected from among




and


In other preferred embodiments the present invention relates to compounds of all the above-mentioned embodiments, wherein

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, $-OCF_3$, $-NR^cR^c$, $-ONR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, 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_{1-6}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 $\mathbf{R^d}$ is a suitable group and is independently selected from among =O, $-OR^e$, C_{1-3}haloalkyloxy, $-OCF_3$, $-NR^eR^e$, $-ONR^eR^e$, $-N(R^g)NR^eR^e$, halogen, $-CF_3$, $-CN$, $-NO_2$, $-S(O)_2R^e$, $-S(O)_2NR^eR^e$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^eR^e$, $-C(O)N(R^g)NR^eR^e$, $-C(O)N(R^g)OR^e$, $-OC(O)R^e$, $-OC(O)NR^eR^e$, $-N(R^g)C(O)R^e$, $-N(OR^g)C(O)R^e$, $-N(R^g)S(O)_2R^e$, $-N(R^g)C(O)OR^e$ and $-N(R^g)C(O)NR^eR^e$;

each $\mathbf{R^e}$ independently denotes hydrogen or a group optionally substituted by one or more, identical or different $\mathbf{R^f}$ and/or $\mathbf{R^g}$, 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 $\mathbf{R^f}$ is a suitable group and is independently selected from among halogen, -OR^g and -CF_3 and

each $\mathbf{R^g}$ 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 **(1a)** and **(1b)** may be combined with one another in any desired manner, thus producing preferred compounds **(1a)** and **(1b)** according to the invention or generic partial amounts of preferred compounds according to the invention **(1a)** and **(1b)**. Each individual embodiment or partial amount defined by this combination is expressly also included and is an object of the invention.

Particularly preferred compounds are:

23 4-[4-((1*R*,2*R*)-1-methanesulphonylamino-indan-2-yloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

24 2-fluoro-4-[4-((1*R*,2*R*)-1-methanesulphonylamino-indan-2-yloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

25 2-fluoro-4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

27 4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

28 2-fluoro-4-[4-((1*R*,2*R*)-2-methanesulphonylamino-cyclopentyloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

29 4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-*N*-((3*S*,4*S*)-3-methoxy-1-methyl-piperidin-4-yl)-benzamide

31 2-fluoro-4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-((3*S*,4*S*)-3-methoxy-1-methyl-piperidin-4-yl)-benzamide

74 2-chloro-4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclohexyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-

benzamide

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

77 4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclohexyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-*N*-(4-methyl-piperazin-1-yl)-benzamide

79 3-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-4-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

84 2-chloro-4-{5-chloro-4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

85 4-{5-chloro-4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-pyrimidin-2-ylamino}-2-fluoro-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

88 4-{5-chloro-4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-pyrimidin-2-ylamino}-2-fluoro-5-methoxy-*N*-(4-methyl-piperazin-1-yl)-benzamide

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

100 2-chloro-4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(4-methyl-piperazin-1-yl)-benzamide

101 2-fluoro-4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(4-methyl-piperazin-1-yl)-benzamide

102 2-chloro-4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

103 2-fluoro-4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

104 2-fluoro-4-[4-((1*R*,2*R*)-2-methanesulphonylamino-cyclohexyloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

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

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

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

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-methyl-pentyl; *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.

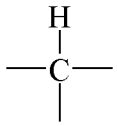
By the terms propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl etc. without any further definition are meant saturated hydrocarbon groups with the corresponding number of carbon atoms, all the isomeric forms being included.

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.

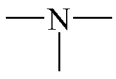
By the terms butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, nonadienyl, decadienyl etc. without any further definition are meant unsaturated hydrocarbon groups with the corresponding number of carbon atoms and two double bonds, all the isomeric forms, i.e. (*Z*)/(*E*) isomers, being included 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-dimethylamino-propyl); diethylaminomethyl; diethylaminoethyl (1-diethylaminoethyl, 2-diethylaminoethyl); diethylaminopropyl (1-diethylaminopropyl, 2- diethylamino-propyl, 3-diethylaminopropyl); diisopropylaminoethyl (1-diisopropylaminoethyl, 2-di-isopropylaminoethyl); bis-2-methoxy-ethylamino; [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.

monocyclic saturated hydrocarbon rings:

cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; cycloheptyl etc.

monocyclic unsaturated hydrocarbon rings:

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.

saturated and unsaturated bicyclic hydrocarbon rings:

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.

Carbobicyclic ring systems comprise bicyclic carbon rings with at least one aromatic ring, such as for example bicyclooctatrienyl, indanyl, 1,2,3,4-tetrahydronaphthyl and 6,7,8,9-tetrahydrobenzocycloheptyl.

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, bi- or polycyclic ring systems 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.

bicyclic and 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; dihydrobenz-isothiazinyl; benzopyranyl; benzothiopyranyl; coumarinyl; isocoumarinyl; chromonyl; chromanonyl; tetrahydroquinolinyl; dihydroquinolinyl; dihydroquinolinonyl; dihydroiso-quinolinonyl; 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.

Heterobicyclic ring systems comprise for example dihydrobenzofuryl, dihydroiso-benzofuryl, dihydroindolyl dihydroisoindolyl, dihydrobenzothiophenyl, dihydroisobenzothio-phenyl, dihydroindazolyl, 1,2-benzisoxazolyl, 1*H*-1,2-benzisoxazolyl, 1,2-benzothiazolyl, 2,3-tetrahydro-1*H*-isoquinolinyl, 3,4-tetrahydro-2*H*-isoquinolinyl, tetrahydroquinolinyl, chromanyl, isochromanyl, isochromenyl, thiochromanyl, thiochromenyl, dihydro-2*H*-phthalazinyl, tetrahydrocinnolinyl, tetrahydroquinazolinyl, tetrahydrobenzodiazepinyl and tetrahydrobenzoxazepinyl.

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.

monocyclic heterorings (saturated and unsaturated):

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; 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

Bu	butyl
c	concentration
cHex	cyclohexane
d	day(s)

TLC	thin layer chromatography
DCM	dichloromethane
DIPEA	*N*-ethyl-*N*,*N*-diisopropylamine (Hünig base)
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulphoxide
EA	ethyl acetate
ESI	electron spray ionization
Et	ethyl
EtOH	ethanol
h	hour(s)
hex	hexyl
HPLC	high performance liquid chromatography
i	iso
IR	infrared spectroscopy
Me	methyl
MeOH	methanol
min	minute(s)
MPLC	medium pressure liquid chromatography
MS	mass spectrometry
NMP	*N*-methylpyrrolidone
NP	normal phase
Pd_2dba_3	tris (dibenzylideneacetone)dipalladium(0)
Ph	phenyl
rac	racemic
R_f (Rf)	retention factor
RP	reversed phase
RT	ambient temperature
temp.	temperature
tert.	tertiary
THF	tetrahydrofuran
$t_{Ret.}$	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

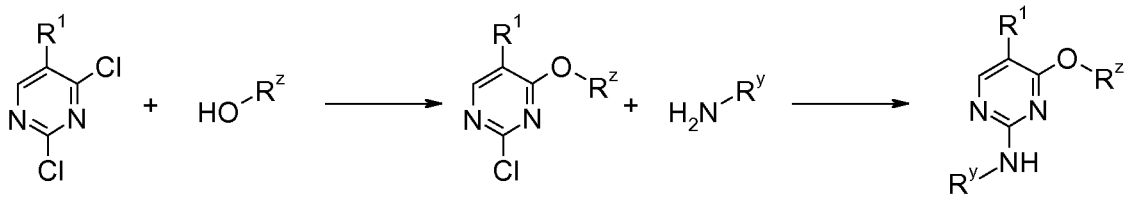
Fragmentor:	70	
Gain EMV:	Threshold: 1 mAU; Stepsize: 2 nm; UV: 220-320 nm	
Injection:	Standard 1 µL	
Flow:	1.0 mL/min	
Column temp.:	35 °C	
Gradient:	0.00 min:	2 % solvent B
	0.00 – 3.50 min:	2 % → 98 % solvent B
	3.50 – 6.00 min:	98 % solvent B

Method F

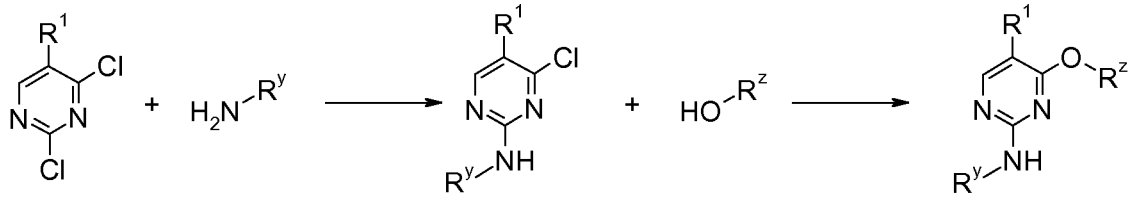
Column:	Phenomenex Gemini C18, 3.0 µm, 2.0 x 50 mm,	
Eluant:	A: H_2O with 0.1 % HCOOH; B: acetonitrile with 0.1 % HCOOH	
Detection:	MS: Positive and negative mode	
Mass range:	100 – 800 m/z	
Fragmentor:	70	
Gain EMV:	Threshold: 1 mAU; Stepsize: 2 nm; UV: 220-320 nm	
Injection:	Standard 1 µL	
Flow:	1.0 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



A-1 **A-2** **I**



A-1 **A-3** **I**

Example compounds of **type I** are prepared from 2,4-dichloropyrimidines **A-1** substituted by $\mathbf{R^1}$, by nucleophilic aromatic substitution using an alcohol $\mathbf{R^z}$-OH and an amine $\mathbf{R^z}$-NH_2. The order of substitution depends to a great extent on the nucleophiles used, the reaction conditions (acidic or basic reaction conditions and the addition of Lewis acids) and the substituent $\mathbf{R^1}$. $\mathbf{R^y}$ and $\mathbf{R^z}$ 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, Cs_2CO_3 or NaH or an acid such as for example HCl. The amines $\mathbf{R^y}$-NH_2 used, and the alcohols $\mathbf{R^z}$-OH are commercially obtainable or are synthesised according to methods known from the literature. The 2-amino-4-oxo-pyrimidines 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 2-amino-4-oxo-pyrimidines of **type I**. Thus, for example, the groups $\mathbf{R^y}$ and $\mathbf{R^z}$ of directly obtainable 2-amino-4-oxo-pyrimidines of **type I**, which consist of a carboxylic acid-, sulphonic acid-, halogen- or amino-substituted aryl, heteroaryl, cycloalkyl or heterocycloalkyl, may be modified by reactions of substitution (at the heteroaryl itself), alkylation, acylation, amination or addition.

Preparation of the starting compounds

If their preparation is not described, the starting materials are commercially obtainable, known from the literature or easily obtainable by the skilled man using general methods, for example

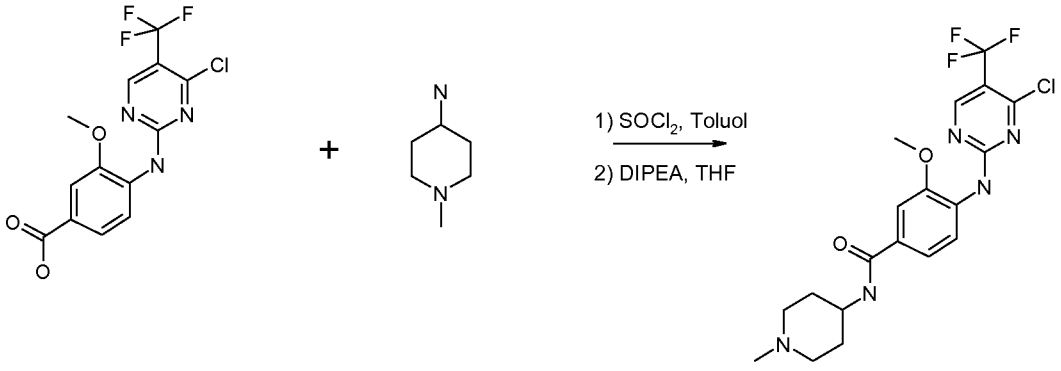
4-amino-2-chloro-5-methoxy-benzoic acid, 4-amino-2-fluoro-5-methoxy-benzoic acid (WO 2008/003958);

4-(4-chloro-5-trifluoromethyl-pyrimidin-2-yl-amino)-3-methoxy-benzoic acid, 4-(4-chloro-5-trifluoromethyl-pyrimidin-2-yl-amino)-2-chloro-5-methoxy-benzoic acid and 4-(4-chloro-5-trifluoromethyl-pyrimidin-2-yl-amino)-2-fluoro-5-methoxy-benzoic acid (analogously to WO 2007/003596);

tert-butyl 4-benzylamino-3-fluoro-piperidine-1-carboxylate (*J. Med. Chem.* **1999**, 42(12), 2087-2104);

benzyl (3*S*,4*S*)-4-*tert*-butoxycarbonylamino-3-hydroxy-piperidine-1-carboxylate and benzyl (3*R*,4*R*)-4-*tert*-butoxycarbonylamino-3-hydroxy-piperidine-1-carboxylate (WO 2004/058144).

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

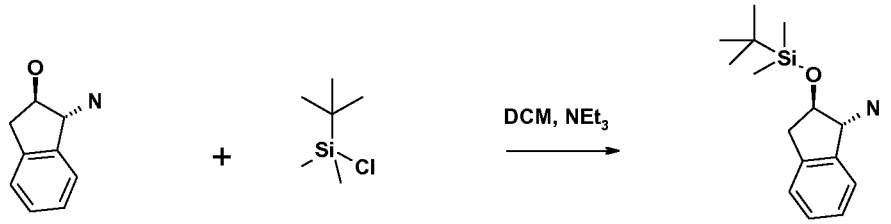


4-(4-chloro-5-trifluoromethyl-pyrimidin-2-ylamino)-benzoic acid (2.0 g) is suspended in 70 mL toluene, mixed with thionyl chloride (0.84 mL) and heated to 120 °C for 2 h with stirring. The reaction mixture is left to cool to RT and the solvent is eliminated using the rotary evaporator. The residue is suspended in 50 mL THF, cooled to 0 °C and a solution of 4-amino-1-methylpiperidine (0.66 g) and DIPEA (1.97 mL), dissolved in 20 mL THF, is added dropwise. The reaction mixture is slowly brought up to RT and stirred for a further

12 h at RT. The reaction mixture is cooled to 0 °C, the product is filtered off and used without any further purification.

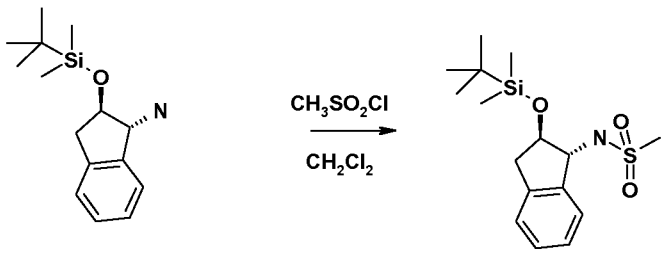
_N_-((1_R_,2_R_)-2-hydroxy-indan-1-yl)-_N_-methyl-methanesulphonamide

a) (1_R_,2_R_)-2-(*tert*-butyl-dimethyl-silanyloxy)-indan-1-ylamine



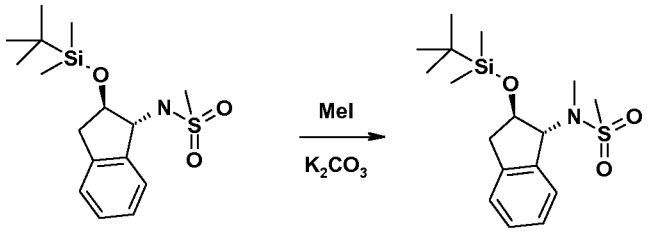
(1_R_,2_R_)-1-amino-2-indanol (2.00 g) is suspended in 20 mL DCM and combined with triethylamine (3.61 mL) as well as DMAP (0.32 g). Then *tert*-butyldimethylchlorosilane (4.04 g in 2 mL CH_2Cl_2) is added. The reaction mixture is stirred for 16 h at RT and, once the reaction is complete, it is mixed with water, extracted with CH_2Cl_2 and the organic phase is freed from the solvent using the rotary evaporator. The residue is taken up in MeOH and isolute is added. After elimination of the solvent once again the mixture is purified by normal phase chromatography (CH_2Cl_2/EA). The product-containing fractions are combined and freed from the solvent using the rotary evaporator.

b) _N_-[(1_R_,2_R_)-2-(*tert*-butyl-dimethyl-silanyloxy)-indan-1-yl]-methanesulphonamide



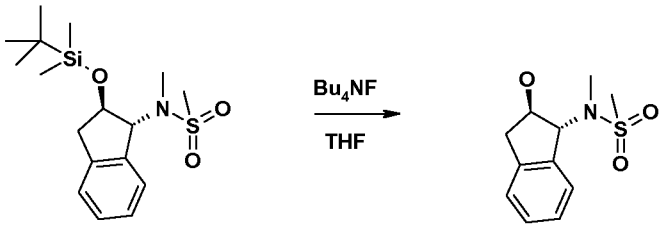
(1_R_,2_R_)-2-(*tert*-butyl-dimethyl-silanyloxy)-indan-1-ylamine (1.60 g) is dissolved in 16 mL DCM and combined with triethylamine (2.54 mL). Then methanesulphonyl chloride (0.61 mL in 5mL DCM) is added dropwise. The reaction mixture is stirred for 2 h and after elimination of the solvent it is purified by normal phase chromatography (cHex/EA). The product-containing fractions are combined and freed from the solvent using the rotary evaporator.

c) *N*-[(1*R*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-indan-1-yl]-*N*-methyl-methanesulphonamide



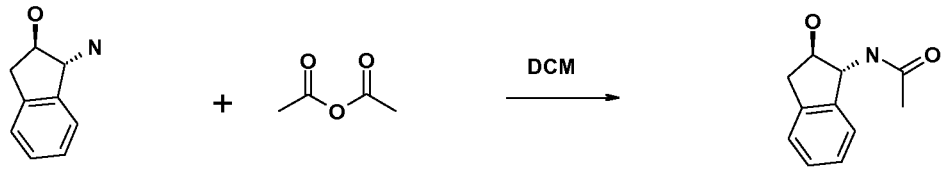
N-[(1*R*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-indan-1-yl]-methanesulphonamide (0.50 g) is dissolved in 2 mL DMF and mixed with Cs_2CO_3 (0.96 g, 2.93 mmol) and MeI (0.10 mL). The reaction mixture is stirred for 2 h and, once the reaction has ended, combined with DCM and NaOH (1 N). The organic phase is dried on $MgSO_4$ and freed from the solvent using the rotary evaporator. After dissolving in acetonitrile water is added. The precipitate formed is filtered off, washed with water and taken up in DCM. After drying on $MgSO_4$ the solvent is eliminated using the rotary evaporator.

d) *N*-((1*R*,2*R*)-2-hydroxy-indan-1-yl)-*N*-methyl-methanesulphonamide



N-[(1*R*,2*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-indan-1-yl]-*N*-methyl-methanesulphonamide (0.53 g) is dissolved in 5 mL THF, combined with Bu_4NF (5mL of a 1 N solution in THF) and stirred for 2 h at RT. After the reaction is complete the reaction mixture is freed from the solvent. After the addition of CH_2Cl_2 it is extracted with HCl (aqu., 1 N). The organic phase is dried on $MgSO_4$. After elimination of the solvent the mixture is purified by normal phase chromatography (CH_2Cl_2, MeOH). The product-containing fractions are combined and freed from the solvent using the rotary evaporator.

***N*-((1*R*.2*R*)-2-hydroxy-indan-1-yl)-acetamide**

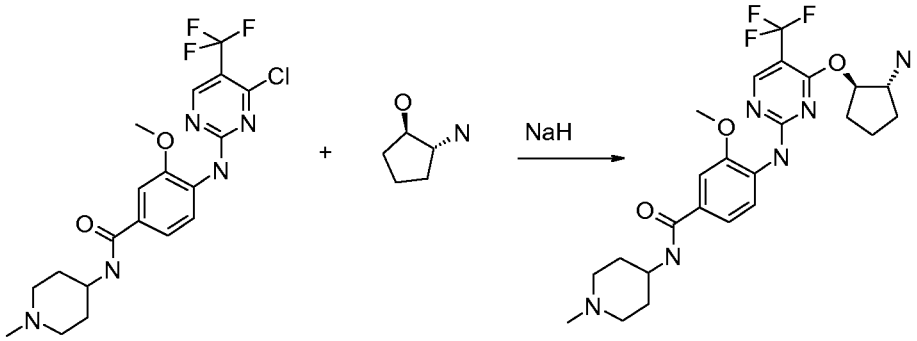


(1*R*,2*S*)-1-amino-2-indanol (2.0 g) is suspended in 100 mL CH_2Cl_2 and at RT combined with acetic anhydride (1.27 mL). The reaction mixture is stirred for 1 h at RT. After the reaction has ended the solvent is eliminated using the rotary evaporator and the crude product (HPLC-MS: $t_{Ret.}$ = 0.81 min; MS $(M+H)^+$ = 192) is used in subsequent reactions without further purification.

Preparation of the End Compounds

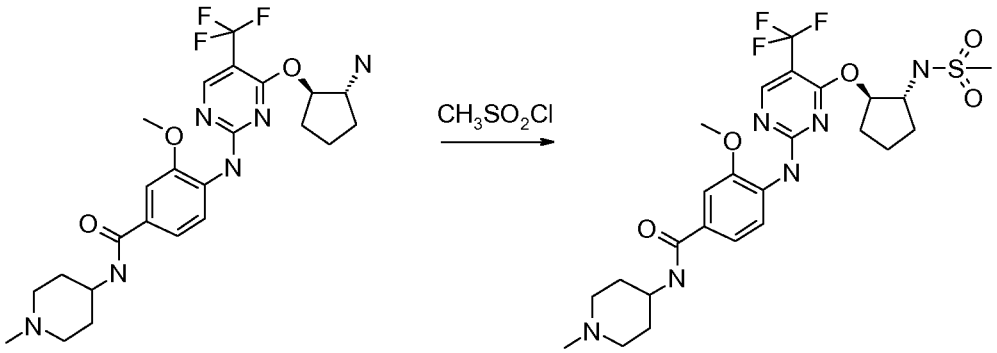
Example 26: 4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

a) 4-[4-((1*R*,2*R*)-2-amino-cyclopentyloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide



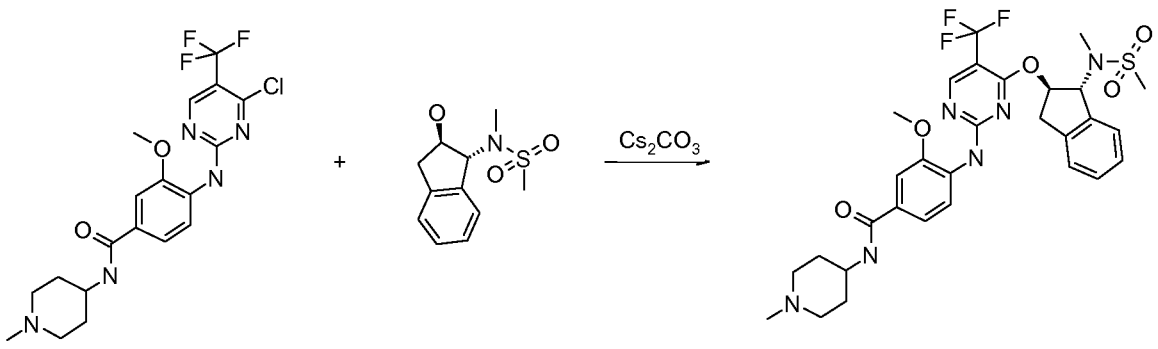
(*R*,*R*)-2-aminocyclopentanol x HCl (155 mg) is added to a suspension of NaH (135.2 mg) in dioxane (0.75 mL) and stirred for 30 min at RT. Then 4-(4-chloro-5-trifluoromethyl-pyrimidin-2-ylamino)-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide (250 mg) is added. After 18 h, H_2O (50 mL) is added. The precipitate formed is filtered off, washed with H_2O, dissolved in CH_2Cl_2 and extracted with aqueous $KHSO_4$ solution (10 %). The aqueous phase is made basic again with K_2CO_3 and extracted with CH_2Cl_2. The organic phase is dried on magnesium sulphate, filtered to remove the desiccant and the solvent is eliminated in vacuo.

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



4-[4-((1*R*.2*R*)-2-amino-cyclopentyloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide (0.26 g) is dissolved in 4 mL CH_2Cl_2 and mixed with DIPEA (0.11 mL). Then methanesulphonyl chloride (0.05 mL) is added. The reaction mixture is stirred for 18 h and purified by preparative HPLC without any further pre-purification. The product-containing fractions are combined and freed from the solvent by freeze-drying.

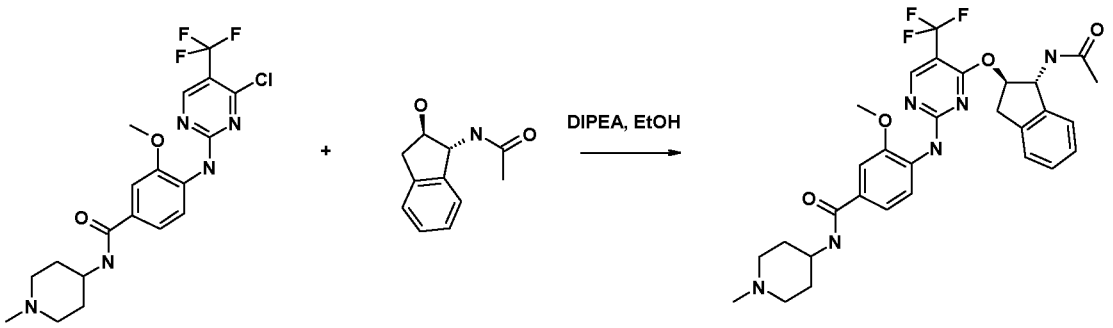
Example 27: 4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoro-methyl-pyrimidin-2-ylamino}-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide



4-(4-chloro-5-trifluoromethyl-pyrimidin-2-ylamino)-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide (50 mg) and *N*-((1*R*,2*R*)-2-amino-indan-1-yl)-methanesulphonamide *N*-((1*R*,2*R*)-2-hydroxy-indan-1-yl)-*N*-methyl-methanesulphonamide (54.4 mg) are suspended in dioxane (0.6 mL), mixed with Cs_2CO_3 (184 mg) as well as some $MgSO_4$ and stirred overnight at 85 °C. The reaction mixture is left to cool to RT, MeOH and isolute are added

thereto and the solvent is eliminated using the rotary evaporator. Purification is carried out by preparative HPLC.

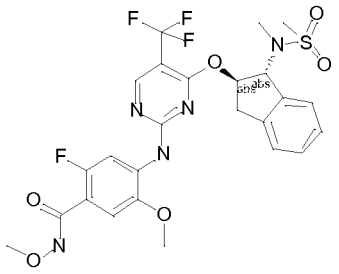
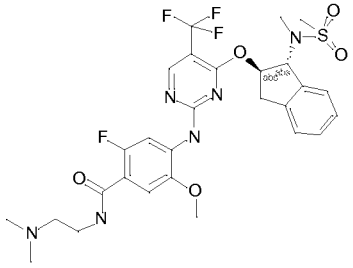
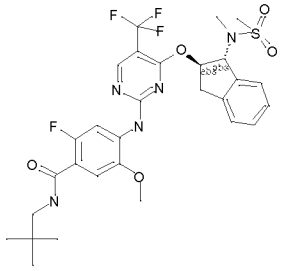
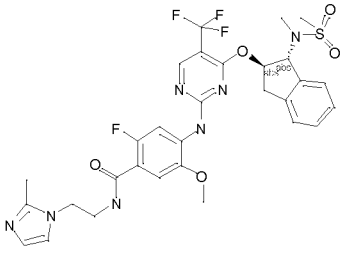
Example 68: 4-[4-((1*R*,2*R*)-1-acetylamino-indan-2-yloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

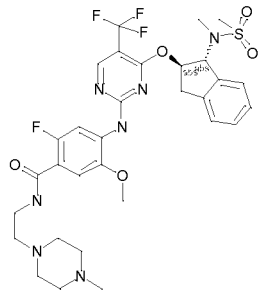
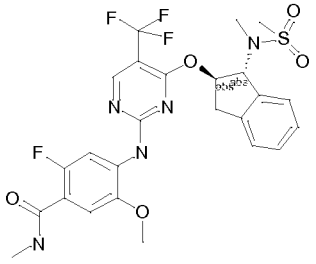
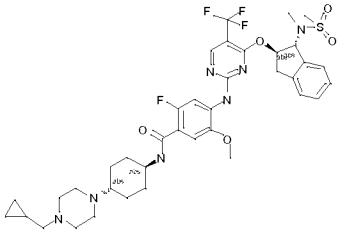
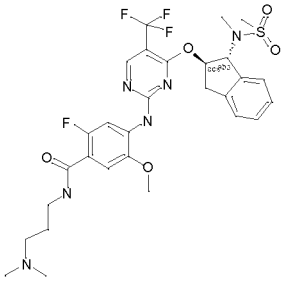
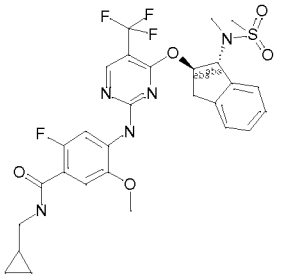


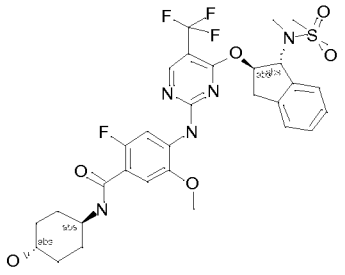
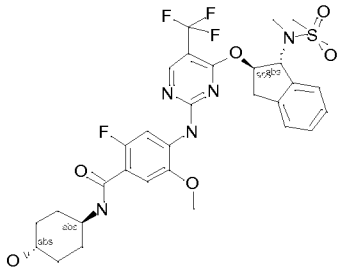
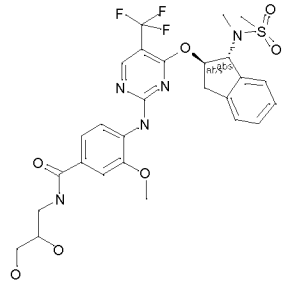
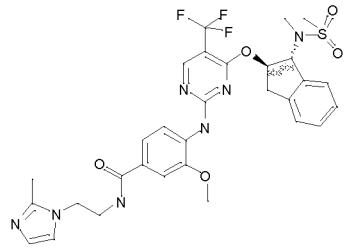
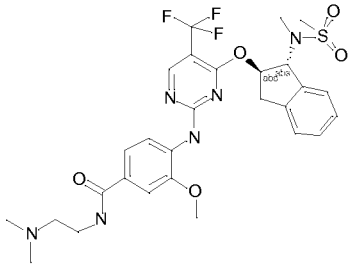
N-((1*R*,2*R*)-2-hydroxy-indan-1-yl)-acetamide (43 mg) and 4-(4-chloro-5-trifluoromethyl-pyrimidin-2-ylamino)-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide (50 mg) are suspended in 0.70 mL dioxane, mixed with Cs_2CO_3 (184 mg) and some $MgSO_4$ and stirred overnight at 85 °C. The reaction mixture is allowed to cool to RT and the solvent is eliminated using the rotary evaporator. The residue is taken up in MeOH and purified by preparative HPLC. The product-containing fractions are freeze-dried.

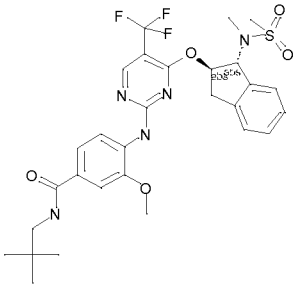
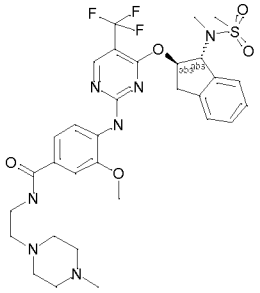
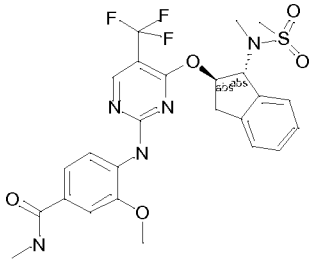
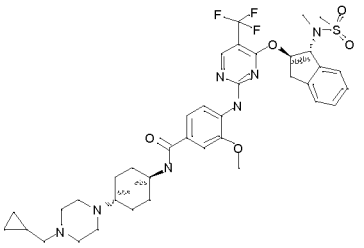
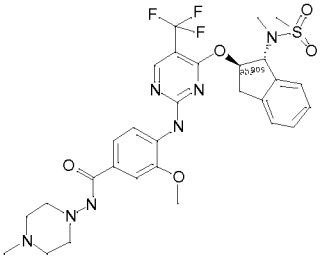
Analogously to the syntheses in Examples 26, 27 and 68 as described above, the following Examples in the Table and comparable additional examples may be obtained from the corresponding precursors, which are either commercially obtainable or are obtained by methods known from the literature.

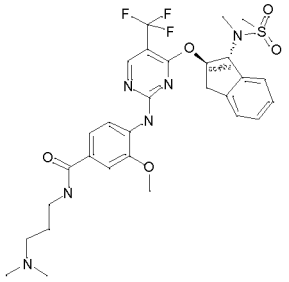
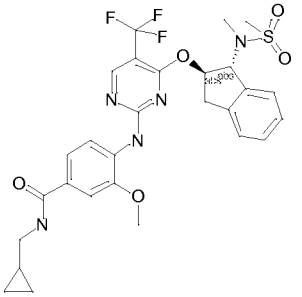
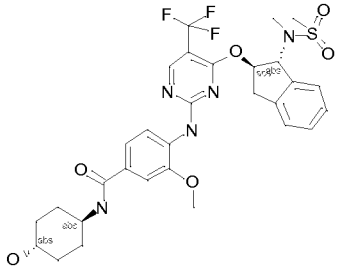
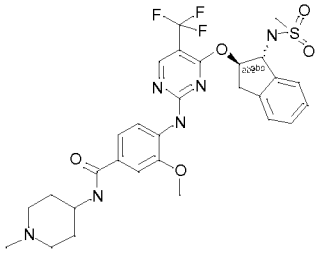
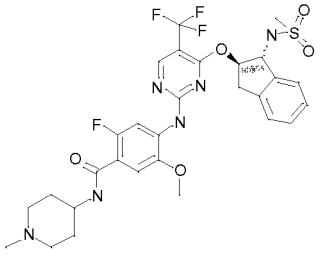
Table 1: Examples 1 – 111

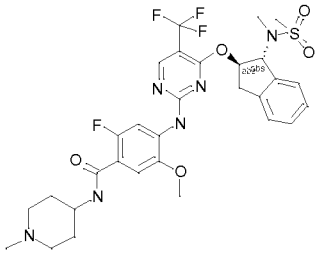
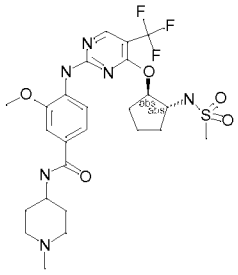
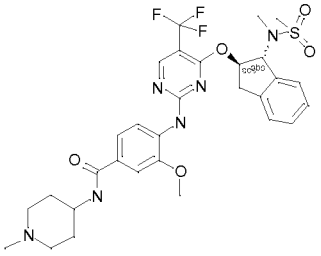
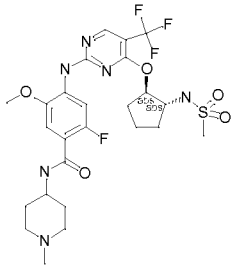
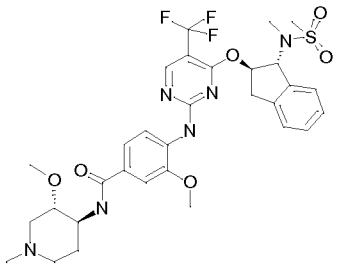
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2		641	2.12
3		640	2.38
4		678	1.99

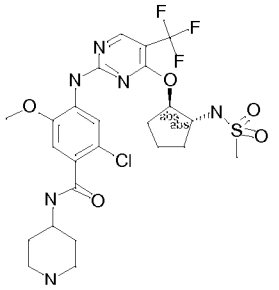
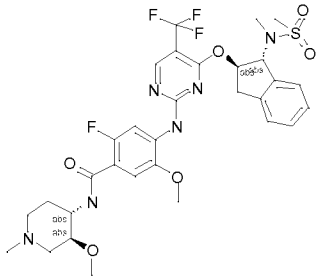
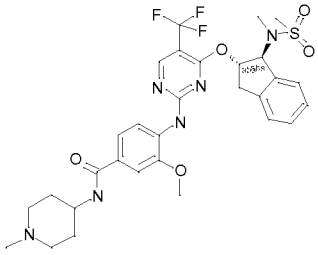
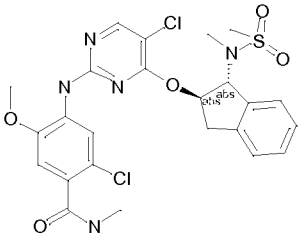
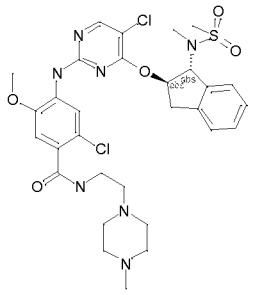
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7		790	2.26
8		655	2.16
9		624	2.24

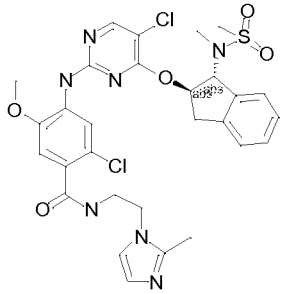
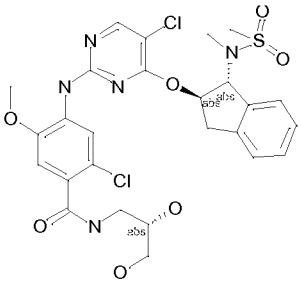
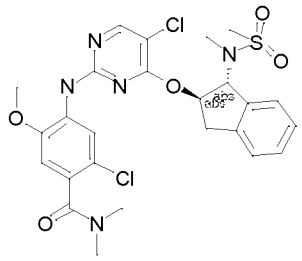
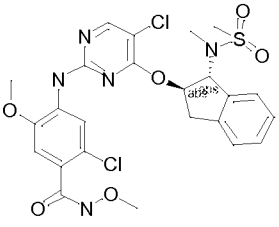
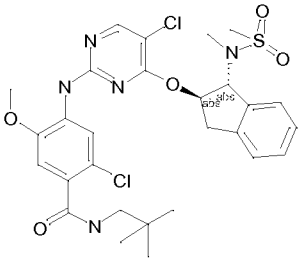
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
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12		626	1.82
13		660	1.92
14		623	1.85

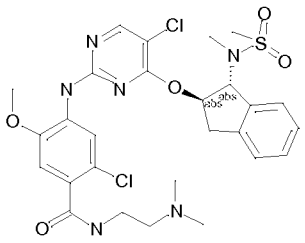
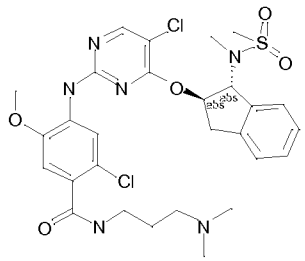
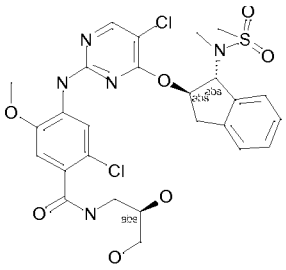
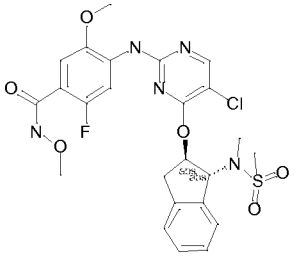
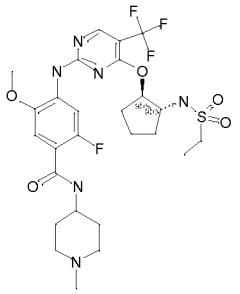
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
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16		678	1.77
17		566	1.76
18		772	2.00
19		650	1.70

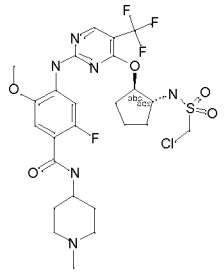
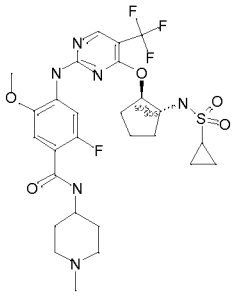
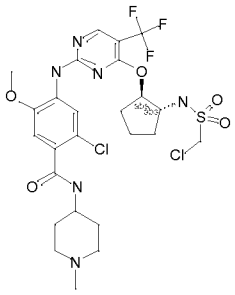
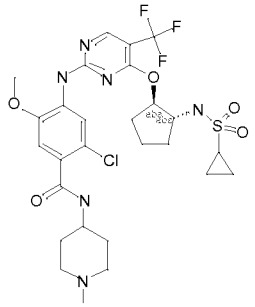
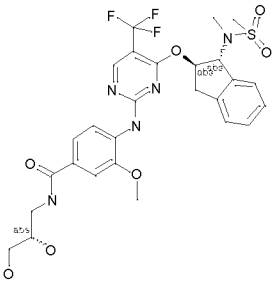
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
20		637	2.11
21		606	2.12
22		650	1.97
23		635	1.96
24		653	2.01

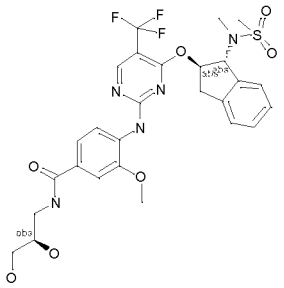
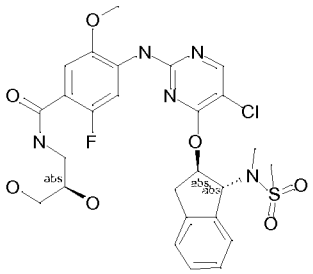
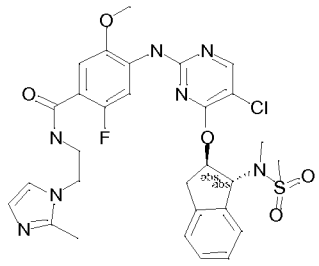
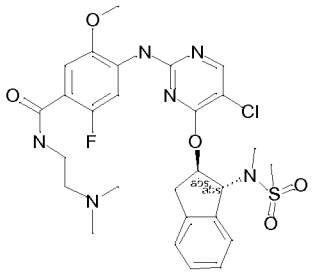
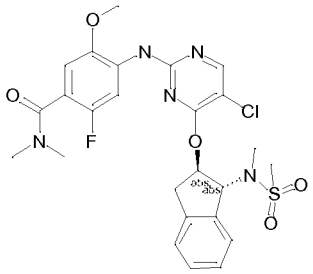
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
25		667	2.10
26		587	1.80
27		649	1.99
28		605	1.89
29		679	1.94

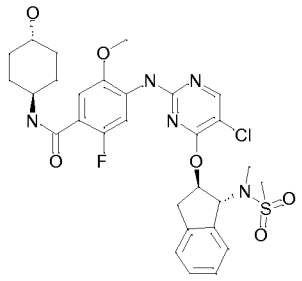
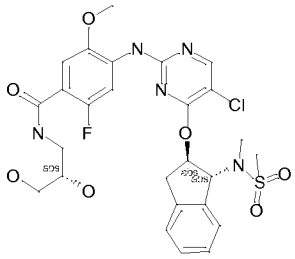
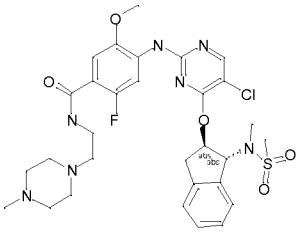
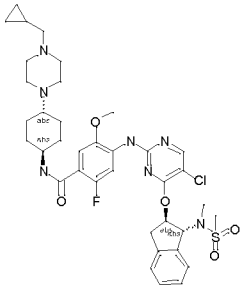
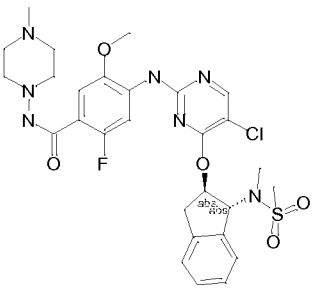
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
30		621	1.87
31		697	2.08
32		649	1.98
33		532	1.88
34		678	1.92

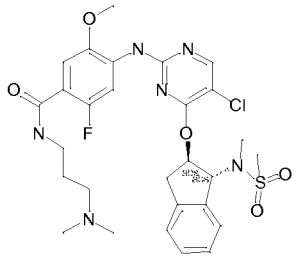
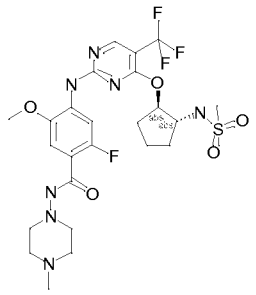
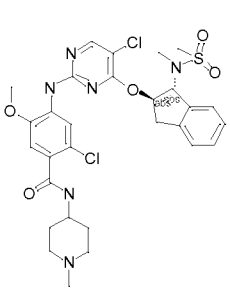
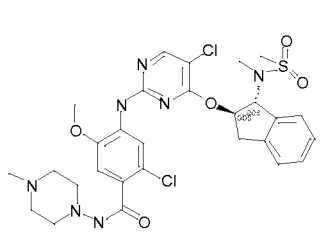
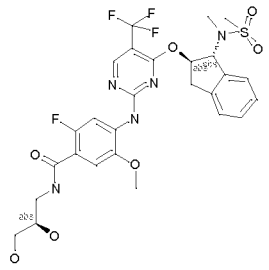
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
35		660	1.87
36		626	1.77
37		580	2.02
38		582	1.50
39		622	2.20

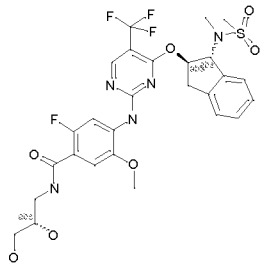
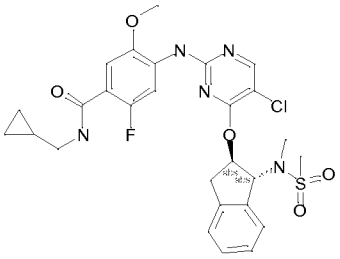
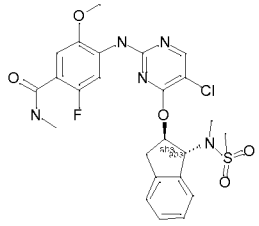
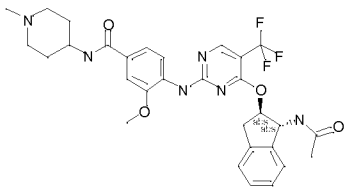
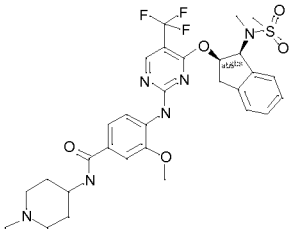
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
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41		637	2.02
42		626	1.77
43		566	1.69
44		619	2.05

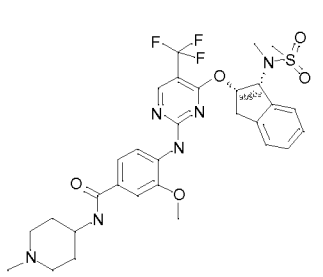
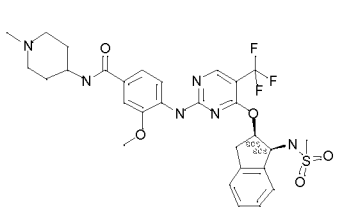
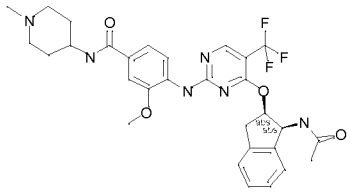
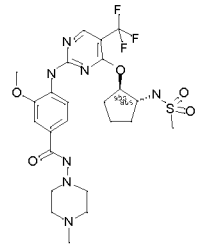
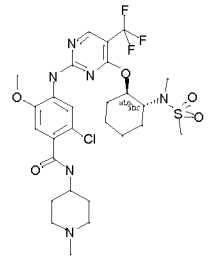
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
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46		631	2.04
47		655	1.92
48		647	1.96
49		626	1.82

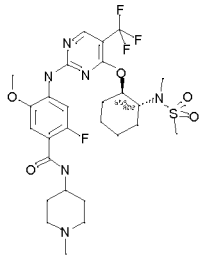
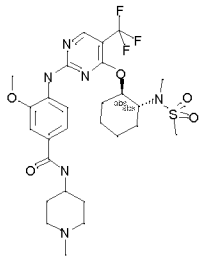
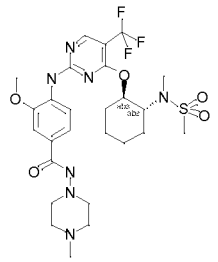
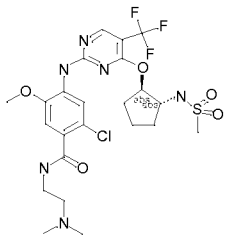
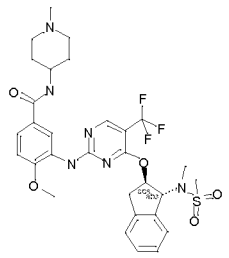
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
50		626	1.82
51		610	1.83
52		644	1.91
53		607	2.06
54		564	2.02

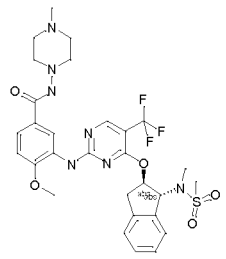
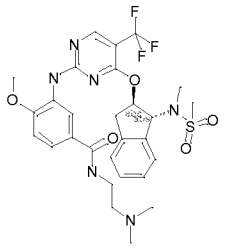
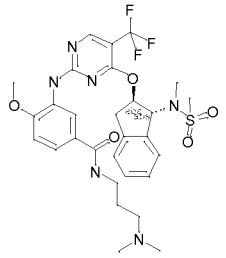
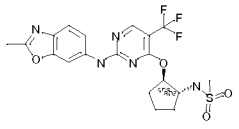
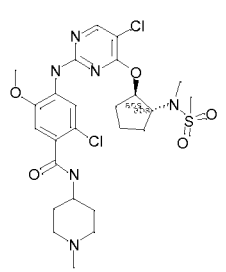
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
55		634	1.97
56		608	1.80
57		662	1.98
58		756	2.22
59		634	1.88

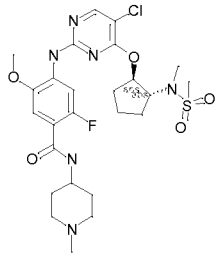
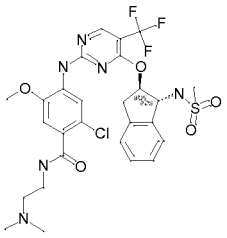
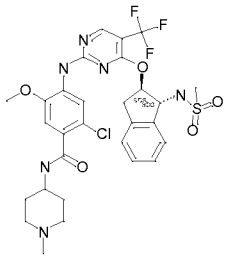
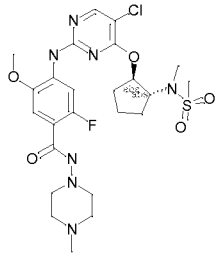
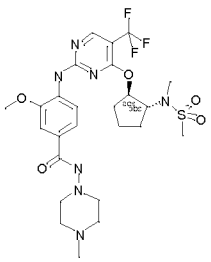
No.	Structure	MS (M+H)$^+$	t_{Ret} [min]
60		621	2.18
61		606	1.77
62		649	1.97
63		650	1.85
64		644	1.88

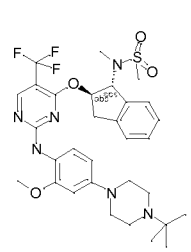
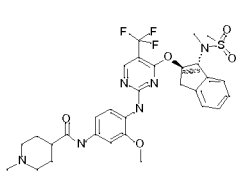
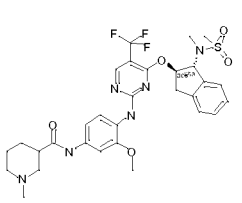
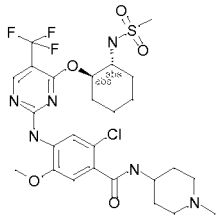
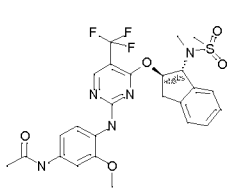
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
65		644	1.87
66		590	2.31
67	Chiral 	550	2.06
68	Chiral 	599	1.83
69	Chiral 	649	2.00

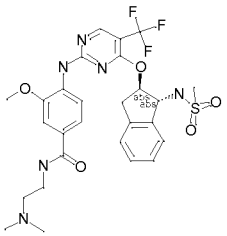
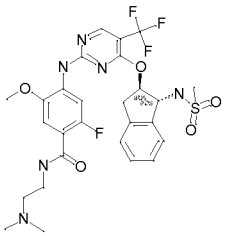
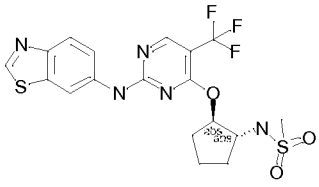
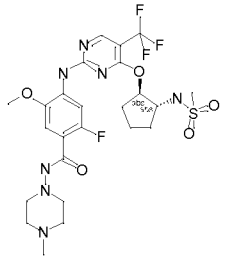
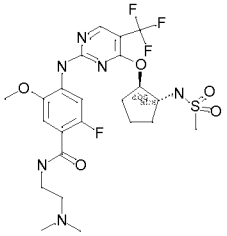
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
70	Chiral 	649	1.99
71	Chiral 	635	1.85
72	Chiral 	599	1.84
73	Chiral 	588	1.66
74	Chiral 	649	1.93

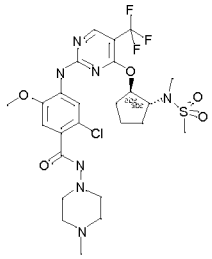
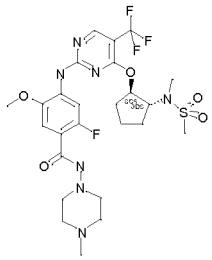
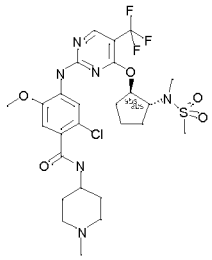
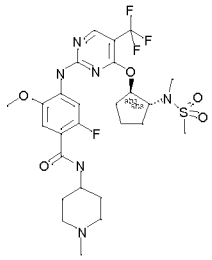
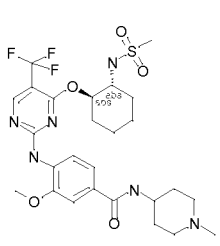
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
75	Chiral 	633	1.98
76	Chiral 	615	1.90
77	Chiral 	616	1.76
78	Chiral 	595	1.87
79	Chiral 	649	1.95

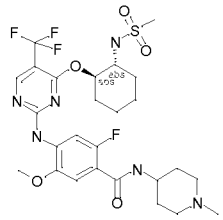
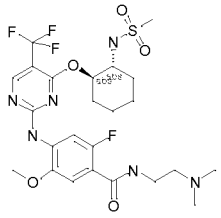
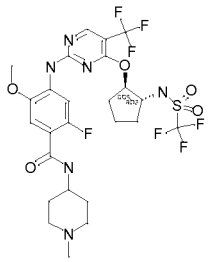
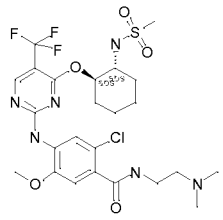
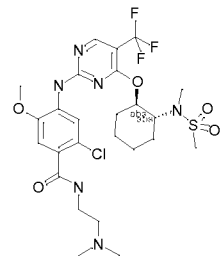
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
80	Chiral 	650	1.82
81	Chiral 	623	1.96
82	Chiral 	637	2.01
83	Chiral 	472	1.82
84	Chiral 	601	1.84

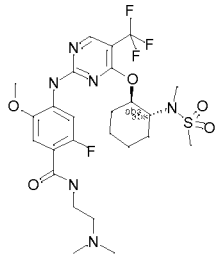
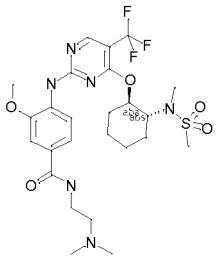
No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
85	Chiral 	585	1.89
86	Chiral 	643	1.98
87	Chiral 	669	2.06
88	Chiral 	586	1.73
89	Chiral 	602	1.72

No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
90		649	2.35
91		649	2.04
92		649	2.12
93		635	1.85
94		566	1.94

No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
95	Chiral 	609	1.90
96	Chiral 	627	2.02
97	Chiral 	474	1.82
98	Chiral 	606	1.73
99	Chiral 	579	2.02

No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
100	Chiral 	636	1.85
101	Chiral 	620	1.81
102	Chiral 	635	1.89
103	Chiral 	619	2.04
104	Chiral 	601	1.82

No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
105	Chiral 	619	1.90
106	Chiral 	593	1.92
107	Chiral 	659	1.48
108	Chiral 	609	1.86
109	Chiral 	623	1.96

No.	Structure	MS $(M+H)^+$	t_{Ret} [min]
110	Chiral 	607	2.00
111	Chiral 	589	1.90

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 lists the IC_{50} values of the example compounds 1 – 111 as obtained by determining from Assay 1 or Assay 2 (*). The inhibitory effect of compounds according to the invention is sufficiently demonstrated thereby.

Table 2

No.	PTK2 1 h IC_{50} [nM]
1	6
2	5
3	3
4	5
5	4
6	17
7	8
8	4
9	19
10	7
11	7
12	4
13	4
14	3
15	11
16	4
17	13
18	4
19	4
20	3
21	12
22	8

No.	PTK2 1 h IC_{50} [nM]
23	3
24	1
25	2
26	1
27	1
28	2
29	3
30	1
31	3
32	400
33	7
34	2
35	2
36	3
37	28
38	1
39	6
40	3
41	2
42	4
43	22
44	6

No.	PTK2 1 h IC_{50} [nM]
45	5
46	34
47	3
48	22
49	5
50	4
51	13
52	6
53	4
54	92
55	6
56	9
57	2
58	6
59	6
60	3
61	4
62	3
63	3
64	6
65	10
66	16

No.	PTK2 1 h IC_{50} [nM]
67	16
68	2
69	42
70	238
71	17
72	174
73	2
74	0.42
75	0.31
76	0.29
77	0.3
78	0.37
79	0.4*
80	0.41
81	0.31

No.	PTK2 1 h IC_{50} [nM]
82	0.38
83	1
84	0.32
85	0.37
86	0.45
87	0.28
88	0.37
89	0.33
90	0.85*
91	4
92	3
93	0.42
94	5
95	0.56
96	0.54

No.	PTK2 1 h IC_{50} [nM]
97	2
98	4
99	0.37
100	0.26
101	0.3
102	0.61
103	0.28
104	0.32
105	0.39
106	1
107	103
108	0.44
109	0.35
110	0.35
111	0.36

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 passaged twice a week. The test is carried out in 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 seeded in 60 µL F12 Kaighn's (10 % FCS) with the addition of 0.3 % agarose (37°C). After cooling to RT for 1 h the test compounds (30 µL from serial dilutions) are added for quadruple measurements. The concentration of the test compounds usually covers a test range of between 10 µM and 0.3 nM. The compounds (stock solution: 10 mM in 100 % DMSO) are prediluted in F12 Kaighn's Medium + 6% DMSO, to obtain a final concentration of 1 % 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, 18 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 18 µL of Alamar Blue reduced by autoclaving and 180 µL of F12 Kaighn's Medium (10 % FCS). 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 passaged twice a week.

For the test, 2 x 10^4 cells pro well/90 µL 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 (10 µL from serial dilution) are added the next day. The concentration of the test compounds usually covers a range of 50 µM and 0.8 nM. The test compounds

(stock solution: 10 mM in 100 % DMSO) are diluted in medium/medium 10% DMSO such that the final concentration is 1 % 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 150 µL 4 % formaldehyde in D-PBS for 20 min at RT. (The cell lawn is washed five times with 200 µl of 0.1% Triton X-100 in D-PBS) for 5 min each time and then incubated for 90 min with 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 1:200 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 five times with 100 µl 0.1% Tween in D-PBS for 5 min in each case 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 five times with 100 µl of 0.1% Tween in D-PBS for 5 min in each case. 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 to 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.

Example compounds 1 - 100 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 **(1a)** or **(1b)**, 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 **(1a)** and **(1b)** 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.

Other possible combination partners are 2-chlorodesoxyadenosine, 2-fluorodesoxy-cytidine, 2-methoxyoestradiol, 2C4, 3-alethin, 131-I-TM-601, 3CPA, 7-ethyl-10-hydroxycamptothecin, 16-azaepothilon B, A 105972, A 204197, aldesleukin, alitretinoin, altretamin, alvocidib, amonafid, anthrapyrazole, AG-2037, AP-5280, apaziquon, apomin, aranose, arglabin, arzoxifen, atamestan, atrasentan, auristatin PE, AVLB, AZ10992, ABX-EGF, ARRY-300, ARRY-142886/AZD-6244, ARRY-704/AZD-8330, AS-703026, azacytidin, azaepothilon B, azonafid, BAY-43-9006, BBR-3464, BBR-3576, bevacizumab, biricodar dicitrate, BCX-1777, bleocin, BLP-25, BMS-184476, BMS-247550, BMS-188797, BMS-275291, BNP-1350, BNP-7787, BIBW 2992, BIBF 1120, bleomycinic acid, bleomycin A, bleomycin B, bryostatin-1, bortezomib, brostallicin, busulphan, CA-4 prodrug, CA-4, CapCell, calcitriol, canertinib, canfosfamid, capecitabin, carboxyphthalatoplatin, CCI-779, CEP-701, CEP-751, CBT-1cefixim, ceflatonin, ceftriaxon, celecoxib, celmoleukin, cemadotin, CH4987655/RO-4987655, chlorotrianisen, cilengitid, ciclosporin, CDA-II, CDC-394, CKD-602, clofarabin, colchicin, combretastatin A4, CHS-828, CLL-Thera, CMT-3cryptophycin 52, CTP-37, CP-461, CV-247, cyanomorpholinodoxorubicin, cytarabin, D 24851, decitabin, deoxorubicin, deoxyrubicin, deoxycoformycin, depsipeptid, desoxyepothilon B, dexamethasone, dexrazoxanet, diethylstilbestrol, diflomotecan, didox, DMDC, dolastatin 10, doranidazole, E7010, E-6201, edatrexat, edotreotid, efaproxiral, eflornithin, EKB-569, EKB-509, elsamitrucin, epothilon B, epratuzumab, ER-86526, erlotinib, ET-18-OCH3, ethynylcytidin, ethynyloestradiol, exatecan, exatecan mesylate, exemestan, exisulind, fenretinid, floxuridin, folic acid, FOLFOX, FOLFIRI, formestan, galarubicin, gallium maltolate, gefinitib, gemtuzumab, gimatecan, glufosfamid, GCS-IOO, G17DT immunogen, GMK, GPX-100, GSK-5126766, GSK-1120212, GW2016, granisetron, hexamethylmelaminr, histamine, homoharringtonin, hyaluronic acid, hydroxyurea, hydroxyprogesterone caproate, ibandronat, ibritumomab, idatrexat, idenestrol, IDN-5109, IMC-1C11, immunol, indisulam, interferon alpha-2a, interferon alfa-2b, interleukin-2, ionafarnib, iproplatin, irofulven, isohomohalichondrin-B, isoflavone, isotretinoin, ixabepilon, JRX-2, JSF-154, J-107088, conjugated oestrogens, Kahalid F, ketoconazole, KW-2170, lobaplatin, leflunomid, lenograstim, leuprolid, leuporelin, lexidronam, LGD-1550, linezolid, lutetium-texaphyrin, lometrexol, losoxantron, LU 223651, lurtotecan, mafosfamid, marimastat, mechloroethamin, methyltestosterone,

methylprednisolone, MEN-10755, MDX-H210, MDX-447, MGV, midostaurin, minodronic acid, mitomycin, mivobulin, MK-2206, MLN518, motexafin-gadolinium, MS-209, MS-275, MX6, neridronat, neovastat, nimesulid, nitroglycerine, nolatrexed, norelin, N-acetylcysteine, 06-benzylguanine, omeprazole, oncophage, ormiplatin, ortataxel, oxantrazole, oestrogen, patupilon, pegfilgrastim, PCK-3145, PEG-filgrastim, PBI-1402, PEG-paclitaxel, PEP-005, P-04, PKC412, P54, PI-88, pelitinib, pemetrexed, pentrix, perifosin, perillylalcohol, PG-TXL, PG2, PLX-4032/RO-5185426, PT-100, picoplatin, pivaloyloxymethylbutyrate, pixantron, phenoxodiol O, PKI166, plevitrexed, plicamycin, polyprenic acid, porfiromycin, prednisone, prednisolone, quinamed, quinupristin, RAF-265, ramosetron, ranpirnase, RDEA-119/BAY 869766, rebeccamycin analogues, revimid, RG-7167, rhizoxin, rhu-mab, risedronat, rituximab, rofecoxib, Ro-31-7453, RO-5126766, RPR 109881A, rubidazon, rubitecan, R-flurbiprofen, S-9788, sabarubicin, SAHA, sargramostim, satraplatin, SB 408075, SU5416, SU6668, SDX-101, semustin, seocalcitol, SM-11355, SN-38, SN-4071, SR-27897, SR-31747, SRL-172, sorafenib, spiroplatin, squalamin, suberanilohydroxamic acid, sutent, T 900607, T 138067, TAS-103, tacedinalin, talaporfin, tariquitar, taxotere, taxoprexin, tazaroten, tegafur, temozolamid, tesmilifen, testosterone, testosterone propionate, tetraplatin, tetrodotoxin, tezacitabin, thalidomide, theralux, therarubicin, thymectacin, tiazofurin, tipifarnib, tirapazamin, tocladesin, tomudex, toremofin, trabectedin, transMID-107, transretinoic acid, traszutumab, tretinoin, triacetyluridine, triapin, trimetrexate, TLK-286TXD 258, urocidin, valrubicin, vatalanib, vincristin, vinflunin, virulizin, WX-UK1, vectibix, xeloda, XELOX, XL-281, XL-518/R-7420, YM-511, YM-598, ZD-4190, ZD-6474, ZD-4054, ZD-0473, ZD-6126, ZD-9331, ZDI839, zoledronate and zosuquidar.

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 **(1a)(1b)**	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 **(1a)(1b)**	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.

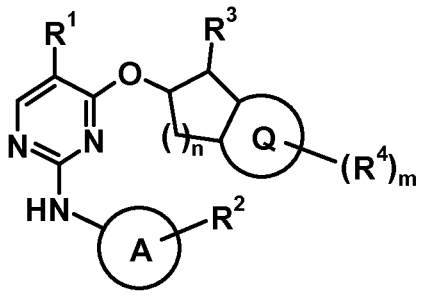
C) Ampoule solution

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

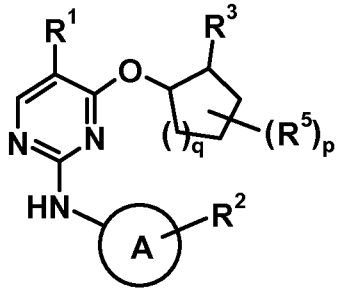
The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by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

Claims

1. Compounds of general formula **(1a)** and **(1b)**



(1a)



(1b)

,

wherein

A denotes a group, optionally substituted by one or more, identical or different $\mathbf{R^2}$, selected from among C_{3-10}cycloalkyl, 3-8 membered heterocycloalkyl, C_{6-15}aryl and 5-12 membered heteroaryl;

Q denotes a group, optionally substituted by one or more, identical or different $\mathbf{R^4}$, selected from among phenyl and 5-6 membered heteroaryl;

$\mathbf{R^1}$ denotes a group selected from among halogen, $-OR^c$, $-OCF_3$, $-SR^c$, $-NR^cR^c$, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, C_{1-3}alkyl, C_{1-3}haloalkyl and C_{1-3}haloalkyloxy;

$\mathbf{R^2}$, $\mathbf{R^4}$ and $\mathbf{R^5}$ 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 $\mathbf{R^b}$;

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

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 each 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** is a suitable group and each 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,

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

each $\mathbf{R^e}$ independently denotes hydrogen or a group optionally substituted by one or more, identical or different $\mathbf{R^f}$ and/or $\mathbf{R^g}$ 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 $\mathbf{R^f}$ is a suitable group and each is independently selected from among halogen and $-CF_3$;

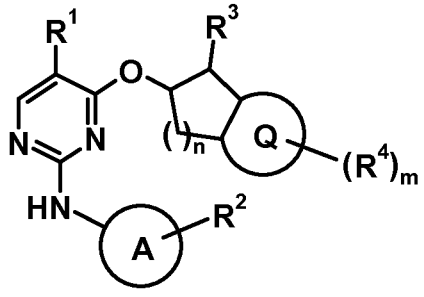
each $\mathbf{R^g}$ independently denotes hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{4-11}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 2-6 membered heteroalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkyl, 5-12 membered heteroaryl or 6-18 membered heteroarylalkyl;

m and **p** independently of one another denote 0, 1, 2 or 3 and

n and **q** denote 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 salts thereof, particularly the pharmacologically acceptable acid addition salts thereof.

2. Compounds of general formula **(1a)** according to claim 1



(1a)

,

wherein

R^1, **R^2**, **R^3**, **R^4**, **A**, **Q**, **n** and **m** are defined as in claim 1.

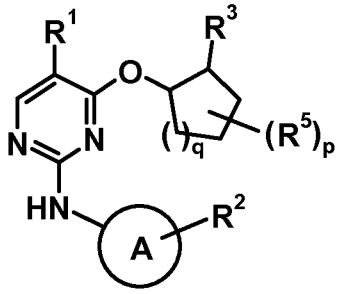
3. Compounds according to claim 2, wherein

n is 1.

4. Compounds according to one of claims 1 to 3, wherein

m is equal to 0.

5. Compounds of general formula **(1b)** according to claim 1



(1b) ,

wherein

R^1, **R^2**, **R^3**, **R^5**, **A**, **p** and **q** are defined as in claim 1.

6. Compounds according to claim 5, wherein

q is equal to 1 or 2.

7. Compounds according to one of claims 5 or 6, wherein

p is equal to 0.

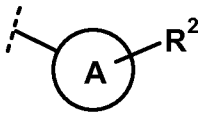
8. Compounds according to one of claims 1 to 7, wherein

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

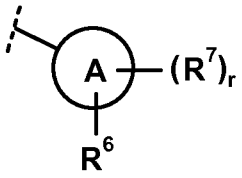
R^c and R^g are defined as in claim 1.

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

the group



denotes



,

R^6 and R^7 are defined as R^2 in claim 1,

r is equal to 1 or 2 and

A is defined as in claim 1.

10. Compounds according to claim 9, wherein

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

R^6, R^7 and **r** are defined as in claim 9.

11. Compounds according to claim 10, wherein

A is a phenyl;

r has the value 1 or 2;

each R^7 is independently selected from among halogen, C_{1-6}alkyl and C_{1-6}alkoxy and

R^6 is defined as in claim 9.

12. Compounds according to one of claims 9 to 11, wherein

R^6 is selected from among hydrogen, R^{a2}, R^{b2} and R^{a2} substituted by one or more, identical or different R^{b2} and/or 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 $\mathbf{R^{d2}}$ is a suitable substituent and is independently selected from among $-OR^{e2}$, $-NR^{e2}R^{e2}$, $-C(O)N(R^{g2})OR^{e2}$ and $-C(O)NR^{e2}R^{e2}$;

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, 5-6 membered heteroaryl 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.

13. Compounds according to claim 1 selected from among

23 4-[4-((1*R*,2*R*)-1-methanesulphonylamino-indan-2-yloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

24 2-fluoro-4-[4-((1*R*,2*R*)-1-methanesulphonylamino-indan-2-yloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

25 2-fluoro-4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

27 4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

28 2-fluoro-4-[4-((1*R*,2*R*)-2-methanesulphonylamino-cyclopentyloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

29 4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-*N*-((3*S*,4*S*)-3-methoxy-1-methyl-piperidin-4-yl)-

benzamide

31 2-fluoro-4-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-((3*S*,4*S*)-3-methoxy-1-methyl-piperidin-4-yl)-benzamide

74 2-chloro-4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclohexyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

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

77 4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclohexyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-3-methoxy-*N*-(4-methyl-piperazin-1-yl)-benzamide

79 3-{4-[(1*R*,2*R*)-1-(methanesulphonyl-methyl-amino)-indan-2-yloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-4-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

84 2-chloro-4-{5-chloro-4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

85 4-{5-chloro-4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-pyrimidin-2-ylamino}-2-fluoro-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

88 4-{5-chloro-4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-pyrimidin-2-ylamino}-2-fluoro-5-methoxy-*N*-(4-methyl-piperazin-1-yl)-benzamide

90 N-((1*R*,2*R*)-2-{2-[4-(4-tert-butyl-piperazin-1-yl)-2-methoxy-phenylamino]-5-trifluoromethyl-pyrimidin-4-yloxy}-indan-1-yl)-*N*-methyl-methanesulphonamid

100 2-chloro-4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(4-methyl-piperazin-1-yl)-benzamide

101 2-fluoro-4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(4-methyl-piperazin-1-yl)-benzamide

102 2-chloro-4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-5-trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

103 2-fluoro-4-{4-[(1*R*,2*R*)-2-(methanesulphonyl-methyl-amino)-cyclopentyloxy]-5-

trifluoromethyl-pyrimidin-2-ylamino}-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

104 2-fluoro-4-[4-((1*R*,2*R*)-2-methanesulphonylamino-cyclohexyloxy)-5-trifluoromethyl-pyrimidin-2-ylamino]-5-methoxy-*N*-(1-methyl-piperidin-4-yl)-benzamide

14. Compounds according to one of claims 1 to 13 – or the pharmaceutically acceptable salts thereof – as medicaments.

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

16. Pharmaceutical preparation containing as active substance one or more compounds according to one of claims 1 to 13 – or the pharmaceutically acceptable salts thereof– optionally in combination with conventional excipients and/or carriers.

17. Pharmaceutical preparation comprising a compound according to one of claims 1 to 13 – or one of the pharmaceutically acceptable salts thereof– and at least one other cytostatic or cytotoxic active substance different from **(1a)** and **(1b)**.