

2,4 (4,6) PYRIMIDINE DERIVATIVES

The human genome encompasses some 2,000 proteins that utilize adenosine 5'-triphosphate (ATP) in one way or another and some 500 of these encode for protein kinases, i.e the protein-tyrosine and protein-serine/threonine kinases, that share a catalytic domain conserved in sequence and structure but which are notably different in how there catalysis is regulated. Substrate phosphorylation by these enzymes is nature's predominant molecular way of organizing cellular signal transduction and regulating biochemical processes in general. It is not surprising, therefore, that abnormal phosphorylation of cellular proteins is a hallmark of disease and that there is a growing interest in the use of kinase inhibitors as drugs for therapeutic intervention in many disease states such as cancer, diabetes, inflammation and arthritis.

In fact the search for such agents has recently culminated in the approval of the first kinase inhibitor drugs Herceptin® (Trastuzumab) and Gleevec™ (imatinib mesylate) for medical use. Herceptin® (Trastuzumab) is targeted against Her2/*neu*, a receptor tyrosine kinase found to be amplified up to 100-fold in about 30% of patients with invasive breast cancer. In clinical trials Herceptin® (Trastuzumab) proved to have anti-tumour activity against breast cancer (Review by L.K. Shawer *et al*, "Smart Drugs: Tyrosine kinase inhibitors in cancer therapy", 2002, Cancer Cell Vol.1, 117), and accordingly provided the proof of principle for therapy targeted to receptor tyrosine kinases. The second example, Gleevec™ (imatinib mesylate), is targeted against the abelson tyrosine kinase (Bcr-Abl), a constitutively active cytoplasmic tyrosine kinase present in virtually all patients with chronic myelogenous leukaemia (CML) and 15% to 30% of adult patients with acute lymphoblastic leukaemia. In clinical trials Gleevec™ (imatinib mesylate) showed a spectacular efficacy with minimal side effects that led to an approval within 3 months of submission. The speed of passage of this agent through clinical trials and regulatory review has become a case study in rapid drug development (Drucker B.J. & Lydon N., "Lessons learned from the development of an Abl tyrosine kinase inhibitor for chronic myelogenous leukaemia.", 2000, J.Clin.Invest. 105, 3).

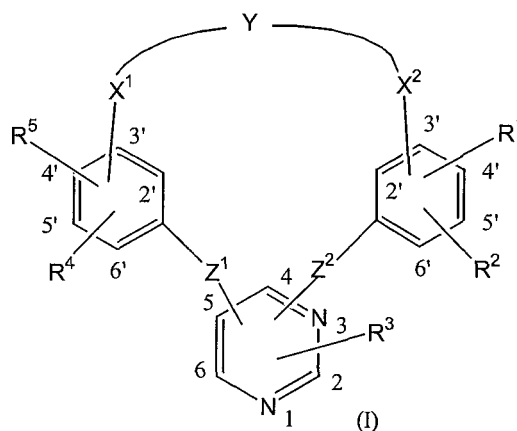
In addition to the above, EGF receptor tyrosine kinases has been shown to be implicated in non-malignant proliferative disorders such as psoriasis (Elder *et al*, Science, 1989, 243; 811). It is therefore expected that inhibitors of EGF type receptor tyrosine kinases will be useful in the treatment of non-malignant diseases of excessive

cellular proliferation such as psoriasis, benign prostatic hypertrophy, atherosclerosis and restenosis.

It is accordingly an object of the present invention to provide further kinase inhibitors useful in the manufacture of medicaments, in particular in the manufacture of medicaments for the treatment of cell proliferative related disorders.

This invention relates to 2,4 (4,6) pyrimidine derived macrocycles of formula (I) that have been found to have kinase inhibitory activity. In particular, the compounds of the present invention were found to have an anti-proliferative activity and are accordingly useful in methods of treatment of the human or animal body, for example in the manufacture of medicaments for use in hyper proliferative disorders such as atherosclerosis, restenosis and cancer. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of anti-proliferative effect .

This invention concerns compounds of formula (I)



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

Z¹ and Z² each independently represents NR²² ; in particular Z¹ and Z² represents NH; in a more particular embodiment Z¹ and Z² are at positions 2,4 or 4,6 of the pyrimidine ring;

Y represents -C₃₋₉alkyl-; -C₃₋₉alkenyl-; -C₃₋₉alkynyl-;

-C₃₋₇alkyl-CO-NH- optionally substituted with amino, mono- or di(C₁₋₄alkyl)amino, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide,

- C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₄alkyloxycarbonylamino-;
 -C₃₋₇alkenyl-CO-NH- optionally substituted with amino, mono- or
 di(C₁₋₄alkyl)amino, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl,
 C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₄alkyloxycarbonylamino- ;
 5 -C₃₋₇alkynyl-CO-NH- optionally substituted with amino, mono- or
 di(C₁₋₄alkyl)amino, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl,
 C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₄alkyloxycarbonylamino-;
 -C₁₋₅alkyl-oxy-C₁₋₅alkyl-; -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-;
 -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-; -C₁₋₆alkyl-CO-NH-; -C₁₋₆alkyl-NH-CO-;
 10 -C₁₋₃alkyl-NH-CS-Het⁹-; -C₁₋₃alkyl-NH-CO-Het³-; C₁₋₂alkyl-CO-Het¹⁰-CO-;
 -Het⁴-C₁₋₃alkyl-CO-NH-C₁₋₃alkyl-; -C₁₋₇alkyl-CO-; -C₁₋₆alkyl-CO-C₁₋₆alkyl-;
 -C₁₋₂alkyl-NH-CO-L¹-NH-; -NH-CO-L²-NH-; -C₁₋₂alkyl-CO-NH-L³-CO-;
 -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-; -C₁₋₂alkyl-NH-CO-L¹-NH-CO-;
 -CO-NH-L²-CO-; -C₁₋₂alkyl-CO-NH-L³-CO-NH-C₁₋₃alkyl-;
 15 -C₁₋₂alkyl-CO-NH-L³-CO-NH-; -C₁₋₂alkyl-CO-NR¹⁰-C₁₋₃alkyl-CO-;
 -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-; -NR¹²-CO-C₁₋₃alkyl-NH-;
 Het⁵-CO-C₁₋₂alkyl-; -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-;
 -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-; -Het⁶-CO-Het⁷-; -Het⁸-NH-C₁₋₃alkyl-CO-NH- ;
 -C₁₋₃alkyl-NH-CO-Het³²-CO- or C₁₋₃alkyl-CO-Het³³-CO-NH-;
 20 X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹⁶,
 -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹⁸,
 -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-, -Het²⁴-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 R¹ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-,
 25 halo-phenyl-carbonylamino-, Het²⁰,
 C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-, or R¹ represents
 C₁₋₆alkyl substituted with one or where possible two or more substituents selected
 from hydroxy, Het¹⁸ or halo;
 R² represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-,
 30 C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or
 di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-,
 aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide,
 C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
 R³ represents hydrogen, cyano, nitro, C₁₋₄alkyl, or C₁₋₄alkyl substituted with one or
 35 more substituents selected from halo, C₁₋₄alkyloxy-, amino-, mono-or
 di(C₁₋₄alkyl)amino-, C₁₋₄alkyl-sulfonyl- or phenyl-;

- R⁴ represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-,
C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or
di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-,
aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide,
5 C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- R⁵ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-,
halo-phenyl-carbonylamino-, Het²¹,
C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-, or R⁵ represents
C₁₋₆alkyl substituted with one or where possible two or more substituents selected
10 from hydroxy, Het¹⁹ or halo;
- R⁶ represents hydrogen, C₁₋₄alkyl, Het¹¹, Het¹²-C₁₋₄alkyl-, phenyl-C₁₋₄alkyl- or phenyl
wherein said R⁶ is optionally substituted with one or where possible two or more
substituents selected from hydroxy, amino or C₁₋₄alkyloxy-;
- R⁷ represents hydrogen, C₁₋₄alkyl, Het¹³-C₁₋₄alkyl- or C₁₋₄alkyloxyC₁₋₄alkyl-;
- 15 R¹⁰, R¹² and R¹³ each independently represent hydrogen, or C₁₋₄alkyl optionally
substituted with hydroxy, amino, mono- or di(C₁₋₄alkyl)amine, phenyl, Het²⁶ or
C₁₋₄alkyloxy-;
- R¹¹ represents hydrogen, C₁₋₄alkyl or represent mono-or di(C₁₋₄alkyl)amino-C₁₋₄alkyl-
carbonyl- optionally substituted with hydroxy, pyrimidinyl, mono- or
20 di(C₁₋₄alkyl)amine or C₁₋₄alkyloxy-;
- R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl,
C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- R¹⁷ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, Het¹⁴, Het¹⁵-C₁₋₄alkyl- or
phenyl-C₁₋₄alkyl-;
- 25 R²² represents hydrogen, C₁₋₄alkyl- optionally substituted with one or where possible
two or three substituents selected from halo, cyano and phenyl;
- L¹ represents C₁₋₈alkyl optionally substituted one or where possible two or more
substituents selected from phenyl, indolyl, thienyl, pyridinyl, methylsulfide,
hydroxy, thiol, cyano, thiazolyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-,
30 hydroxyphenyl, C₁₋₄alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl,
C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amino-, imidazolyl or guanidino; in
particular L¹ represents C₁₋₈alkyl optionally substituted one or where possible two
or more substituents selected from phenyl, indolyl, pyridinyl, methylsulfide,
hydroxy, thiol, cyano, thiazolyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-,
35 hydroxyphenyl, C₁₋₄alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl,
C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amino-, imidazolyl or guanidino;

- L^2 represents C_{1-8} alkyl optionally substituted one or where possible two or more substituents selected from phenyl, indolyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, cyano, thiazolyl, polyhalo C_{1-4} alkyl-phenyl-, C_{1-4} alkyloxy-, hydroxyphenyl, C_{1-4} alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl, C_{3-6} cycloalkyl, amino, mono- or di(C_{1-4} alkyl)-amine-, imidazolyl or guanidino; in particular L^2 represents C_{1-8} alkyl optionally substituted one or where possible two or more substituents selected from phenyl, indolyl, thienyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C_{1-4} alkyl)-amino-, imidazolyl or guanidino;
- L^3 represents C_{1-8} alkyl optionally substituted one or where possible two or more substituents selected from phenyl, indolyl, thienyl, pyridinyl, methylsulfide-, hydroxy, thiol, cyano, thiazolyl, polyhalo C_{1-4} alkyl-phenyl-, C_{1-4} alkyloxy-, hydroxyphenyl-, C_{1-4} alkyloxyphenyl-, aminocarbonyl-, hydroxycarbonyl-, C_{3-6} cycloalkyl, amino, mono- or di(C_{1-4} alkyl)-amino-, imidazolyl or guanidino; in particular L^3 represents C_{1-8} alkyl optionally substituted one or where possible two or more substituents selected from phenyl, indolyl, thienyl, pyridinyl, methylsulfide-, hydroxy, thiol, cyano, hydroxyphenyl-, polyhalo C_{1-4} alkyl-phenyl-, C_{1-4} alkyloxy-, aminocarbonyl-, hydroxycarbonyl-, C_{3-6} cycloalkyl, amino, mono- or di(C_{1-4} alkyl)-amino-, imidazolyl or guanidino;
- Het¹ represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹ is optionally substituted with amino, C_{1-4} alkyl, hydroxy- C_{1-4} alkyl-, phenyl, phenyl- C_{1-4} alkyl-, C_{1-4} alkyl-oxy- C_{1-4} alkyl-, mono- or di(C_{1-4} alkyl)amino- or amino-carbonyl-;
- Het² represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het² is optionally substituted with amino, C_{1-4} alkyl, hydroxy- C_{1-4} alkyl-, phenyl, phenyl- C_{1-4} alkyl-, C_{1-4} alkyl-oxy- C_{1-4} alkyl-, mono- or di(C_{1-4} alkyl)amino- or amino-carbonyl-;
- Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²²-carbonyl, C_{1-4} alkyl, hydroxy- C_{1-4} alkyl- or polyhydroxy- C_{1-4} alkyl-;
- Het⁵ and Het⁶ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁵ and Het⁶ are

- optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het⁷ and Het⁸ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁷ and Het⁸ are
- 5 optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het⁹ and Het¹⁰ each independently represent a heterocycle selected from pyrrolidinyl, pyrrolyl, azetidiny, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁹ and Het¹⁰ are optionally substituted with one or where possible two or more
- 10 substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl
- 15 or polyhydroxy-C₁₋₄alkyl-;
- Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 20 Het¹³ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said
- 25 pyrrolidinyl or piperidinyl is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible
- 30 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁶ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl
- 35 or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible

- two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁸ and Het¹⁹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹⁸ or Het¹⁹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl-, mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- Het²⁰ and Het²¹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het²⁰ or Het²¹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl-, mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- Het²² represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²² is optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²⁵, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-; and
- Het²⁵ and Het²⁶ each independently represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²⁵ and Het²⁶ are optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl, pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het³² and Het³³ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-.

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As used in the foregoing definitions and hereinafter,
- halo is generic to fluoro, chloro, bromo and iodo;

- C₁₋₂alkyl defines methyl or ethyl;
- C₁₋₃alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 3 carbon atoms such as, for example, methyl, ethyl, propyl and the like;
- C₁₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like;
- C₁₋₅alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 5 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, 1-methylbutyl, 2,2-dimethylpropyl, 2,2-dimethylethyl and the like;
- 10 - C₁₋₆alkyl is meant to include C₁₋₅alkyl and the higher homologues thereof having 6 carbon atoms such as, for example hexyl, 1,2-dimethylbutyl, 2-methylpentyl and the like;
- C₁₋₇alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 7 carbon atoms and is meant to include C₁₋₆alkyl and the higher homologues thereof having 7 carbon atoms such as, for example 1,2,3-dimethylbutyl, 1,2-methylpentyl and the like;
- 15 - C₁₋₈alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 8 carbon atoms and is meant to include C₁₋₇alkyl and the higher homologues thereof having 8 carbon atoms such as, for example 2,3-dimethylhexyl, 2,3,4-trimethylpentyl, and the like;
- C₃₋₉alkyl defines straight and branched chain saturated hydrocarbon radicals having from 3 to 9 carbon atoms such as propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl and the like;
- C₂₋₄alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 4 carbon atoms such as, for example vinyl, 2-propenyl, 3-butenyl, 2-butenyl and the like;
- 25 - C₃₋₉alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 9 carbon atoms such as, for example 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-hexenyl and the like;
- 30 - C₂₋₆alkynyl defines straight and branched chain hydrocarbon radicals containing one triple bond and having from 2 to 6 carbon atoms such as, for example, 2-propynyl, 3-butynyl, 2-butynyl, 2-pentynyl, 3-pentynyl, 3-methyl-2-butynyl, 3-hexynyl and the like;
- C₃₋₆cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;
- C₁₋₄alkyloxy defines straight or branched saturated hydrocarbon radicals such as methoxy, ethoxy, propyloxy, butyloxy, 1-methylethyloxy, 2-methylpropyloxy and the like;
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- C₁₋₆alkyloxy is meant to include C₁₋₄alkyloxy and the higher homologues such as methoxy, ethoxy, propyloxy, butyloxy, 1-methylethyloxy, 2-methylpropyloxy and the like;

- polyhydroxy-C₁₋₄alkyl is generic to a C₁₋₄alkyl as defined hereinbefore, having two, three or were possible more hydroxy substituents, such as for example trifluoromethyl.

As used in the foregoing definitions and hereinafter, the term formyl refers to a radical of formula $-\text{CH}(=\text{O})$. When X¹ represent the divalent radical $-\text{O}-\text{N}=\text{CH}-$, said radical is attached with the carbon atom to the R³, R⁴ bearing cyclic moiety of the compounds of formula (I) and when X² represents the divalent radical $-\text{O}-\text{N}=\text{CH}-$, said radical is attached with the carbon atom to the R¹, R² bearing phenyl moiety of the compounds of formula (I).

The heterocycles as mentioned in the above definitions and hereinafter, are meant to include all possible isomeric forms thereof, for instance pyrrolyl also includes 2*H*-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl and 1,3,4-thiadiazolyl; pyranlyl includes 2*H*-pyranlyl and 4*H*-pyranlyl.

Further, the heterocycles as mentioned in the above definitions and hereinafter may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a 1-imidazolyl, 2-imidazolyl, 3-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it is benzothiazolyl, it may be 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl and 7-benzothiazolyl.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, trifluoroacetic, lactic, pyruvic, oxalic, malonic, succinic (i.e. butane-dioic acid), maleic, fumaric, malic, tartaric, citric,

methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

5 The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic base addition salt forms which the compounds of formula (I) are able to form. Examples of such base addition salt forms are, for example, the sodium, potassium, calcium salts, and also the salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, *N*-methyl-*D*-glucamine, hydrabamine, amino acids, e.g. arginine, lysine.

10

Conversely said salt forms can be converted by treatment with an appropriate base or acid into the free acid or base form.

15 The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

20 The term stereochemically isomeric forms as used hereinbefore defines the possible different isomeric as well as conformational forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically and conformationally isomeric forms, said mixtures containing all diastereomers, enantiomers and/or conformers of the basic molecular structure. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are
25 intended to be embraced within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

30

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

35 A first group of compounds are those compounds of formula (I) wherein one or more of the following restrictions apply;
 Z^1 and Z^2 represents NH ;

- Y represents -C₃₋₉alkyl-; -C₃₋₉alkenyl-; -C₃₋₇alkyl-CO-NH- optionally substituted with amino, mono- or di(C₁₋₄alkyl)amino or C₁₋₄alkyloxycarbonylamino-;
 -C₁₋₅alkyl-oxy-C₁₋₅alkyl-; -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-;
 -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-; -C₁₋₆alkyl-CO-NH-; -C₁₋₆alkyl-NH-CO-;
 5 -C₁₋₃alkyl-NH-CS-Het⁹-; -C₁₋₃alkyl-NH-CO-Het³-; C₁₋₂alkyl-CO-Het¹⁰-CO-;
 -Het⁴-CH₂-CO-NH-C₁₋₃alkyl-; -C₁₋₇alkyl-CO-; -C₁₋₆alkyl-CO-C₁₋₆alkyl-;
 -C₁₋₂alkyl-NH-CO-L¹-NH-; -C₁₋₂alkyl-CO-NH-L³-CO-; -CO-NH-L²-CO-;
 -C₁₋₂alkyl-NH-CO-L¹-NH-CO-; -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-CO-;
 -C₁₋₂alkyl-CO-NR¹⁰-C₁₋₃alkyl-CO-; -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-;
 10 -NR¹²-CO-C₁₋₃alkyl-NH-; Het⁵-CO-C₁₋₂alkyl-; -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-;
 ; -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-; -Het⁶-CO-Het⁷-; -Het⁸-NH-C₁₋₃alkyl-CO-NH-;
 C₁₋₃alkyl-NH-CO-Het³²-CO- or C₁₋₃alkyl-CO-Het³³-CO-NH-;
- X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-, NR¹⁶,
 -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 15 X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-, NR¹⁸,
 -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-, -Het²⁴-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
- R¹ represents hydrogen, halo, C₁₋₆alkoxy-, Het²⁰ or R¹ represents
 C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-;
- R² represents hydrogen, halo or hydroxy;
- 20 R³ represents hydrogen, nitro or cyano;
- R⁴ represents hydrogen or halo;
- R⁵ represents hydrogen, halo, C₁₋₆alkoxy-, Het²¹ or R⁵ represents
 C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-;
- R⁶ represents hydrogen;
- 25 R⁷ represents hydrogen, C₁₋₄alkyl, or Het¹³-C₁₋₄alkyl-; in particular R⁷ represents
 hydrogen or Het¹³-C₁₋₄alkyl-;
- R⁸ and R⁹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted
 with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or di(C₁₋₄alkyl)-amino-
 or imidazolyl;
- 30 R¹⁰, R¹² and R¹³ each independently represent hydrogen or C₁₋₄alkyl optionally
 substituted with hydroxy or C₁₋₄alkyloxy;
- R¹¹ represents hydrogen, or C₁₋₄alkyl;
- R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl,
 C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- 35 R¹⁷ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, Het¹⁴, Het¹⁵-C₁₋₄alkyl- or
 phenyl-C₁₋₄alkyl-;

- L^1 represents C_{1-8} alkyl optionally substituted one or where possible two or more substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, thiazolyl, cyano, hydroxyphenyl, polyhalo C_{1-4} alkyl-phenyl-, C_{1-4} alkyloxy-, C_{1-4} alkyloxyphenyl-, aminocarbonyl, C_{3-6} cycloalkyl, amino, mono- or di(C_{1-4} alkyl)-amine-, or imidazolyl; in particular L^1 represents C_{1-8} alkyl optionally substituted one or where possible two or more substituents selected from phenyl, pyridinyl, methylsulfide, hydroxy, thiol, thiazolyl, cyano, hydroxyphenyl, polyhalo C_{1-4} alkyl-phenyl-, C_{1-4} alkyloxy-, C_{1-4} alkyloxyphenyl-, aminocarbonyl, C_{3-6} cycloalkyl, amino, mono- or di(C_{1-4} alkyl)-amine-, or imidazolyl;
- L^2 represents C_{1-8} alkyl optionally substituted one or where possible two or more substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, thiazolyl, cyano, hydroxyphenyl, polyhalo C_{1-4} alkyl-phenyl-, C_{1-4} alkyloxy-, C_{1-4} alkyloxyphenyl-, aminocarbonyl, C_{3-6} cycloalkyl, amino, mono- or di(C_{1-4} alkyl)-amine-, or imidazolyl; in particular L^2 represents C_{1-8} alkyl optionally substituted one or where possible two or more substituents selected from phenyl, thienyl, methylsulfide, hydroxy, or mono- or di(C_{1-4} alkyl)-amino-;
- L^3 represents C_{1-8} alkyl optionally substituted one or where possible two or more substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, thiazolyl, cyano, hydroxyphenyl, polyhalo C_{1-4} alkyl-phenyl-, C_{1-4} alkyloxy-, C_{1-4} alkyloxyphenyl-, aminocarbonyl, C_{3-6} cycloalkyl, amino, mono- or di(C_{1-4} alkyl)-amine-, or imidazolyl; in particular L^3 represents C_{1-8} alkyl optionally substituted one or where possible two or more substituents selected from phenyl, pyridinyl, methylsulfide-, cyano, polyhalo C_{1-4} alkyl-phenyl-, C_{1-4} alkyloxy-, aminocarbonyl-, mono- or di(C_{1-4} alkyl)-amino-, C_{3-6} cycloalkyl, thiazolyl or thienyl;
- Het¹ and Het² each independently represent morpholinyl or pyridinyl, wherein said Het¹ or Het² are optionally substituted with amino, C_{1-4} alkyl, hydroxy- C_{1-4} alkyl-, phenyl, phenyl- C_{1-4} alkyl-, C_{1-4} alkyl-oxy- C_{1-4} alkyl-, mono- or di(C_{1-4} alkyl)amino- or amino-carbonyl-; in particular Het¹ and Het² each independently represent morpholinyl;
- Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or where possible two or more hydroxy or Het²²-carbonyl- substituents;
- Het⁵ and Het⁶ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁵ and Het⁶ are optionally substituted with one or where possible two or more hydroxy substituents;

- Het⁷ and Het⁸ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁷ and Het⁸ are optionally substituted with one or where possible two or more hydroxy substituents;
- 5 Het⁹ and Het¹⁰ each independently represent a heterocycle selected from pyrrolidinyl, pyrrolyl, azetidiny, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁹ and Het¹⁰ are optionally substituted with one or where possible two or more hydroxy or C₁₋₄alkyl substituents;
- 10 Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible
- 15 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹³ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl are optionally substituted with one or where possible
- 20 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl are optionally substituted with one or where possible
- 25 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible
- 30 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁶ is optionally substituted with one or where possible two or more substituents
- 35 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible
- 40 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het²⁰ and Het²¹ each independently represent morpholinyl or pyridinyl;

Het²² represents piperazinyl optionally substituted with C₁₋₄alkyl or hydroxy;
 Het²³ and Het²⁴ each independently represent pyrrolidinyl, decahydroquinolinyl or
 piperidinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where
 possible two or more substituents selected from hydroxy, Het²²-carbonyl- or
 5 C₁₋₄alkyl;
 Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl,
 pyrrolidinyl or piperidinyl.

- 10 Another group of compounds according to the present invention consists of those
 compounds of formula (I) wherein one or more of the following restrictions apply;
 Z¹ and Z² represents NH;
 Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₃₋₇alkyl-CO-NH- optionally substituted with
 amino, mono- or di(C₁₋₄alkyl)amino or C₁₋₄alkyloxycarbonylamino-,
 15 -C₁₋₅alkyl-oxy-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-,
 -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-,
 -C₁₋₃alkyl-NH-CS-Het⁹-, -C₁₋₃alkyl-NH-CO-Het³-, C₁₋₂alkyl-CO-Het¹⁰-CO-,
 -Het⁴-CH₂-CO-NH-C₁₋₃alkyl-, -C₁₋₇alkyl-CO-, -C₁₋₆alkyl-CO-C₁₋₆alkyl-,
 -C₁₋₂alkyl-NH-CO-CR⁸R⁹-NH-, -C₁₋₂alkyl-CO-NH-CR²⁰R²¹-CO-,
 20 -C₁₋₂alkyl-CO-NR¹⁰-C₁₋₃alkyl-CO-, -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-,
 -NR¹²-CO-C₁₋₃alkyl-NH-, Het⁵-CO-C₁₋₂alkyl-,
 -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-, -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-,
 -CO-NH-CR¹⁴R¹⁵-CO-, -Het⁶-CO-Het⁷-, or -Het⁸-NH-C₁₋₃alkyl-CO-NH- ;
 X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-, NR¹⁶,
 25 -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-, NR¹⁸,
 -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-, -Het²⁴-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 R¹ represents hydrogen, halo, C₁₋₆alkoxy-, Het²⁰ or R¹ represents
 C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-;
 30 R² represents hydrogen or halo;
 R³ represents hydrogen, nitro or cyano;
 R⁴ represents hydrogen or halo;
 R⁵ represents hydrogen, halo, C₁₋₆alkoxy-, Het²¹ or R⁵ represents
 C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-;
 35 R⁶ represents hydrogen;
 R⁷ represents hydrogen, C₁₋₄alkyl, or Het¹³-C₁₋₄alkyl-; in particular R⁷ represents
 hydrogen or Het¹³-C₁₋₄alkyl-;

- R⁸ and R⁹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or di(C₁₋₄alkyl)-amino- or imidazolyl;
- R¹⁰, R¹² and R¹³ each independently represent hydrogen or C₁₋₄alkyl optionally substituted with hydroxy or C₁₋₄alkyloxy;
- R¹¹ represents hydrogen, or C₁₋₄alkyl;
- R¹⁴ and R¹⁵ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with mono- or di(C₁₋₄alkyl)-amino-;
- R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- R¹⁷ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, Het¹⁴, Het¹⁵-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- R²⁰ and R²¹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with mono- or di(C₁₋₄alkyl)-amino-;
- Het¹ and Het² each independently represent morpholinyl pyridinyl, wherein said Het¹ or Het² are optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-; in particular Het¹ and Het² each independently represent morpholinyl;
- Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or where possible two or more hydroxy substituents;
- Het⁵ and Het⁶ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁵ and Het⁶ are optionally substituted with one or where possible two or more hydroxy substituents;
- Het⁷ and Het⁸ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁷ and Het⁸ are optionally substituted with one or where possible two or more hydroxy substituents;
- Het⁹ and Het¹⁰ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁹ and Het¹⁰ are optionally substituted with one or where possible two or more hydroxy substituents;
- Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents

selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het¹³ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl are optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl are optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁶ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het²⁰ and Het²¹ each independently represent morpholinyl or pyridinyl; or

Het²³ and Het²⁴ each independently represent pyrrolidinyl, decahydroquinolinyl or piperidinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where possible two or more substituents selected from hydroxy or C₁₋₄alkyl.

A further group of compounds according to the present invention consists of those compounds of formula (I) wherein one or more of the following restrictions apply; Z¹ and Z² represents NH;

Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-, -C₁₋₂alkyl-CO-Het¹⁰-CO-, -C₁₋₃alkyl-NH-CO-Het³-, -Het⁴-C₁₋₃alkyl-CO-NH-C₁₋₃alkyl-, -C₁₋₂alkyl-NH-CO-

- L^1 -NH-, -NH-CO- L^2 -NH-, -C₁₋₂alkyl-CO-NH- L^3 -CO-, -C₁₋₂alkyl-NH-CO- L^1 -NH-CO-C₁₋₃alkyl-, -C₁₋₂alkyl-CO-NH- L^3 -CO-NH-C₁₋₃alkyl-, -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-, Het⁵-CO-C₁₋₂alkyl-, -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-, -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-, -C₁₋₃alkyl-NH-CO-Het³²-CO-, or
 5 -C₁₋₃alkyl-CO-Het³³-CO-NH-;
 X^1 represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷-, Het²³-C₁₋₂alkyl- or C₁₋₂alkyl-;
 X^2 represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, Het²⁴-C₁₋₂alkyl- or C₁₋₂alkyl-;
 10 R^1 represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het¹ or C₁₋₄alkyloxy-;
 R^2 represents hydrogen or halo;
 R^3 represents hydrogen or cyano;
 R^4 represents hydrogen or halo;
 15 R^5 represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het² or C₁₋₄alkyloxy-;
 R^6 represents hydrogen;
 R^7 represents hydrogen;
 R^{11} represents hydrogen or C₁₋₄alkyl-;
 20 R^{13} represents hydrogen;
 R^{16} and R^{18} represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl-;
 R^{17} and R^{19} represent hydrogen;
 L^1 represents C₁₋₈alkyl optionally substituted with one or where possible two or more substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-
 25 , C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl-;
 L^2 represents C₁₋₈alkyl optionally substituted with one or where possible two or more substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl-;
 L^3 represents C₁₋₈alkyl optionally substituted with one or where possible two or more
 30 substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl-;
 Het¹ represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het¹ represents morpholinyl or piperazinyl; more in particular Het¹ represents morpholinyl;
 35 Het² represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het² represents morpholinyl or piperazinyl; more in particular Het² represents morpholinyl;

- Het³ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl; in particular Het³ represents piperazinyl, piperidinyl or pyrrolidinyl;
- Het⁴ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl; in particular Het³ represents piperazinyl or piperidinyl;
- 5 Het⁵ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl, in particular Het⁵ represents piperazinyl or piperidinyl, more in particular Het⁵ represents piperazinyl;
- Het¹⁰ represents piperazinyl, piperidinyl, pyrrolidinyl or azetidiny; in particular Het¹⁰ represents pyrrolidinyl, piperazinyl or azetidiny, more in particular Het¹⁰
- 10 represents azetidiny;
- Het¹⁷ represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl; in particular Het¹⁷ represents morpholinyl or piperazinyl;
- Het²² represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl wherein said Het²² is optionally substituted with C₁₋₄alkyl; in particular Het²² represents morpholinyl or
- 15 piperazinyl wherein said morpholinyl or piperazinyl or optionally substituted with C₁₋₄alkyl; more in particular Het²² represents piperazinyl optionally substituted with C₁₋₄alkyl (methyl);
- Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ are optionally substituted
- 20 with Het²²-carbonyl;
- Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl, in particular Het³² and Het³³ are each independently selected from morpholinyl, piperazinyl or piperidinyl, more in particular Het³² and Het³³ are each independently selected from morpholinyl or
- 25 piperidinyl;

- A further group of compounds according to the present invention consists of those compounds of formula (I) wherein one or more of the following restrictions apply;
- 30 Z¹ and Z² represents NH;
- Y represents -C₃₋₉alkyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-, -C₁₋₂alkyl-CO-Het¹⁰-CO-, -Het⁴-C₁₋₃alkyl-CO-NH-C₁₋₃alkyl-, -C₁₋₂alkyl-CO-NH-L³-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-, -C₁₋₂alkyl-CO-NH-L³-CO-NH-C₁₋₃alkyl-,
- 35 -C₁₋₃alkyl-NH-CO-Het³²-CO- or -C₁₋₃alkyl-CO-Het³³-CO-NH-;

- X^1 represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁶-C₁₋₂alkyl-,
-CO-NR¹⁷-, Het²³-C₁₋₂alkyl- or C₁₋₂alkyl; in particular X^1 represents a direct bond,
O, -O-C₁₋₂alkyl-, -NR¹⁶-C₁₋₂alkyl- or -Het²³-C₁₋₂alkyl-;
- X^2 represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl-,
5 -CO-NR¹⁹-, Het²⁴-C₁₋₂alkyl- or C₁₋₂alkyl; in particular X^2 represents a direct bond,
O, -O-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl- or -Het²⁴-C₁₋₂alkyl-; more in particular X^2
represents O, -O-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl- or -Het²⁴-C₁₋₂alkyl-;
- R^1 represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het¹ or
C₁₋₄alkyloxy-; in particular R^1 represents hydrogen, halo, C₁₋₆alkyloxy- or
10 C₁₋₆alkyloxy- substituted with Het¹;
- R^2 represents hydrogen or halo; in particular R^2 represents hydrogen;
- R^3 represents hydrogen or cyano; in particular R^3 represents hydrogen;
- R^4 represents hydrogen or halo; in particular R^4 represents hydrogen;
- R^5 represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het² or
15 C₁₋₄alkyloxy-; in particular R^5 represents hydrogen or C₁₋₆alkyloxy-;
- R^7 represents hydrogen;
- R^{16} and R^{18} represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl-;
- R^{17} and R^{19} represent hydrogen;
- L^1 represents C₁₋₈alkyl optionally substituted with one or where possible two or more
20 substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-
, C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;
in particular L^1 represents C₁₋₈alkyl optionally substituted with C₃₋₆cycloalkyl;
- L^3 represents C₁₋₈alkyl optionally substituted with one or where possible two or more
substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-
25 , C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;
- Het¹ represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het¹
represents morpholinyl or piperazinyl; more in particular Het¹ represents
morpholinyl;
- Het² represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het²
30 represents morpholinyl or piperazinyl; more in particular Het² represents
morpholinyl;
- Het³ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl; in particular Het³
represents piperazinyl, piperidinyl or pyrrolidinyl; more in particular Het³
represents piperazinyl or piperidinyl;
- 35 Het⁴ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl; in particular Het⁴
represents piperazinyl or piperidinyl;

- Het⁵ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl, in particular Het⁵ represents piperazinyl or piperidinyl, more in particular Het⁵ represents piperazinyl;
- Het¹⁰ represents piperazinyl, piperidinyl, pyrrolidinyl or azetidiny; in particular Het¹⁰ represents pyrrolidinyl, piperazinyl or azetidiny, more in particular Het¹⁰ represents azetidiny;
- Het¹⁷ represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl; in particular Het¹⁷ represents morpholinyl or piperazinyl;
- Het²² represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl wherein said Het²² is optionally substituted with C₁₋₄alkyl; in particular Het²² represents morpholinyl or piperazinyl wherein said morpholinyl or piperazinyl or optionally substituted with C₁₋₄alkyl; more in particular Het²² represents piperazinyl optionally substituted with C₁₋₄alkyl;
- Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ are optionally substituted with Het²²-carbonyl; in particular Het²³ and Het²⁴ each independently represent a heterocycle selected from piperazinyl or piperidinyl wherein said Het²³ and Het²⁴ are optionally substituted with Het²²-carbonyl;
- Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl, in particular Het³² and Het³³ are each independently selected from morpholinyl, piperazinyl or piperidinyl, more in particular Het³² and Het³³ are each independently selected from morpholinyl or piperidinyl;
- Another group of compounds are those compounds of formula (I) wherein one or more of the following restrictions apply;
- Z¹ and Z² represents NH;
- Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-NH-CO-, -C₁₋₃alkyl-NH-CO-Het³-, -C₁₋₂alkyl-NH-COCR⁸R⁹-NH-, -C₁₋₂alkyl-NR¹¹-CH₂CO-NH-C₁₋₃alkyl-, Het⁵-CO-C₁₋₂alkyl-, or -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-;
- X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷- or C₁₋₂alkyl;
- X² represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹- or C₁₋₂alkyl;
- R¹ represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het¹ or C₁₋₄alkyloxy-;

- R^2 represents hydrogen or halo;
 R^3 represents hydrogen or cyano;
 R^4 represents hydrogen or halo;
 R^5 represents hydrogen, halo, C_{1-6} alkyloxy- or C_{1-6} alkyloxy- substituted with Het^1 or
 5 C_{1-4} alkyloxy-;
 R^6 represents hydrogen;
 R^7 represents hydrogen;
 R^8 and R^9 each independently hydrogen or C_{1-4} alkyl;
 R^{11} represents hydrogen or C_{1-4} alkyl;
 10 R^{16} and R^{18} represent hydrogen;
 R^{17} and R^{19} represent hydrogen;
 Het^1 represents morpholinyl;
 Het^2 represents morpholinyl;
 Het^3 represents pyrrolidinyl; or
 15 Het^5 represents piperazinyl

Another group of compounds are those compounds of formula (I) wherein one or more of the following restrictions apply;

- Z^1 and Z^2 represent NH; in a particular embodiment Z^1 and Z^2 are at positions 2,4 or
 20 4,6 of the pyrimidine ring;
 Y represents $-C_{3-9}$ alkyl-, $-C_{3-9}$ alkenyl-, $-C_{1-5}$ alkyl- NR^6 - C_{1-5} alkyl-,
 $-C_{1-5}$ alkyl- NR^7 -CO- C_{1-5} alkyl-, $-C_{1-6}$ alkyl-CO-NH-, $-C_{1-6}$ alkyl-NH-CO-, $-C_{1-2}$ alkyl-
 CO- Het^{10} -CO-, $-C_{1-3}$ alkyl-NH-CO- Het^3 -, $-Het^4$ - C_{1-3} alkyl-CO-NH- C_{1-3} alkyl-,
 $-C_{1-2}$ alkyl-NH-CO- L^1 -NH-, $-NH$ -CO- L^2 -NH-, $-C_{1-2}$ alkyl-CO-NH- L^3 -CO-,
 25 $-C_{1-2}$ alkyl-NH-CO- L^1 -NH-CO- C_{1-3} alkyl-, $-C_{1-2}$ alkyl-CO-NH- L^3 -CO-NH- C_{1-3} alkyl-,
 $-C_{1-2}$ alkyl- NR^{11} -CH₂-CO-NH- C_{1-3} alkyl-, Het^5 -CO- C_{1-2} alkyl-,
 $-C_{1-5}$ alkyl-CO-NH- C_{1-3} alkyl-CO-NH-, $-C_{1-5}$ alkyl- NR^{13} -CO- C_{1-3} alkyl-NH-,
 $-C_{1-3}$ alkyl-NH-CO- Het^{32} -CO-, or $-C_{1-3}$ alkyl-CO- Het^{33} -CO-NH-;
 X^1 represents a direct bond, O, $-O$ - C_{1-2} alkyl-, $-CO$ - C_{1-2} alkyl-, $-NR^{16}$ - C_{1-2} alkyl-,
 30 $-CO$ - NR^{17} -, Het^{23} - C_{1-2} alkyl- or C_{1-2} alkyl;
 X^2 represents a direct bond, O, $-O$ - C_{1-2} alkyl-, $-CO$ - C_{1-2} alkyl-, $-NR^{18}$ - C_{1-2} alkyl-,
 $-CO$ - NR^{19} -, Het^{24} - C_{1-2} alkyl- or C_{1-2} alkyl;
 R^1 and R^5 each independently represent hydrogen, halo, C_{1-6} alkyloxy- or C_{1-6} alkyloxy-
 substituted with Het^1 or C_{1-4} alkyloxy-;
 35 R^2 and R^4 each independently represent hydrogen or halo;
 R^3 represents hydrogen or cyano;
 R^6 , R^7 , R^{13} , R^{17} and R^{19} represent hydrogen;

R¹¹ represents hydrogen or C₁₋₄alkyl;

R¹⁶ and R¹⁸ represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl-;

L¹, L² and L³ each independently represents C₁₋₈alkyl optionally substituted with one or where possible two or more substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;

Het¹, Het², Het¹⁷ each independently represent morpholinyl, oxazolyl, isoxazolyl, or piperazinyl;

Het³, Het⁴, Het⁵ each independently represent morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl;

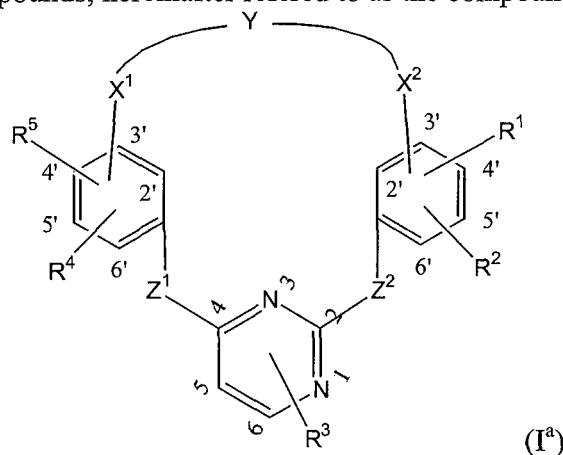
Het¹⁰ represents piperazinyl, piperidinyl, pyrrolidinyl or azetidiny;

Het²² represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl wherein said Het²² is optionally substituted with C₁₋₄alkyl;

Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ are optionally substituted with Het²²-carbonyl;

Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl.

In a further object, the present invention provides the 2,4-pyrimidine derivatives of the formula (I) compounds, hereinafter referred to as the compounds of formula



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein Y, Z¹, Z², X¹, X², R¹, R², R³, R⁴ and R⁵ are defined as for the compounds of formula (I) hereinbefore, including any of the limitations as provided for the different groups of compounds of formula (I) as defined hereinbefore.

In particular those compounds of formula (I^a) wherein one or more of the following restrictions apply;

Z¹ and Z² represents NH;

Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₁₋₆alkyl-CO-NH-,

5 -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₃alkyl-NH-CO-Het³- or
 -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-; in particular Y represents C₃₋₉alkyl-,
 -C₃₋₉alkenyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₃alkyl-NH-CO-Het³- or
 -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-

10 X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, -NR¹⁶-C₁₋₂alkyl-, Het²³-C₁₋₂alkyl or
 -CO-NR¹⁷-; in particular X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, or
 -CO-NR¹⁷-

 X² represents a direct bond, O, -O-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl-, Het²⁴-C₁₋₂alkyl or
 -CO-NR¹⁹-; in particular X² represents a direct bond, O, -O-C₁₋₂alkyl-, or
 -CO-NR¹⁹-;

15 R¹ represents hydrogen, halo, C₁₋₆alkoxy-, or R¹ represents
 C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-; in particular R¹ represents
 hydrogen or halo;

 R² represents hydrogen or halo;

 R³ represents hydrogen, or cyano;

20 R⁴ represents hydrogen or halo;

 R⁵ represents hydrogen, halo, C₁₋₆alkoxy-, or R⁵ represents
 C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-;

 R⁷ represents hydrogen;

 R¹¹ represents hydrogen or C₁₋₄alkyl-;

25 R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl-;

 R¹⁷ represents hydrogen;

 R¹⁹ represents hydrogen;

 Het³ represents pyrrolidinyl;

 Het¹⁷ represents morpholinyl or piperazinyl wherein said Het¹⁷ is optionally substituted
 with C₁₋₄alkyl;

30 Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl
 or piperazinyl.

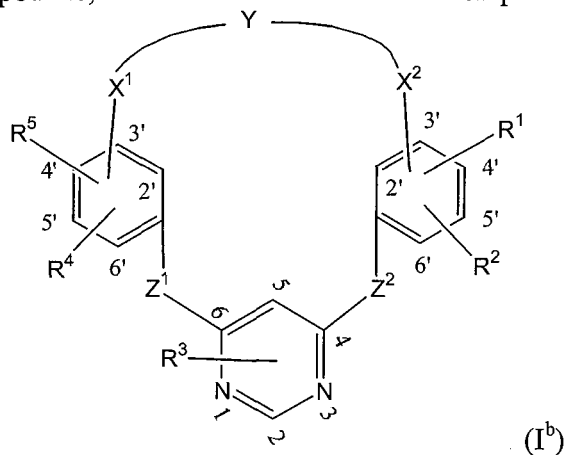
A further group of compounds according to the present invention consists of those

35 compounds of formula (I^a) wherein one or more of the following restrictions apply;

 Z¹ and Z² represents NH;

- Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-,
 -C₁₋₆alkyl-NH-CO-, -C₁₋₃alkyl-NH-CO-Het³- or
 -C₁₋₂alkyl-NR¹¹-CH₂CO-NH-C₁₋₃alkyl-;
- X¹ represents a direct bond, O, -NR¹⁶-C₁₋₂alkyl- or C₁₋₂alkyl-;
- 5 X² represents a direct bond, O, -NR¹⁸-C₁₋₂alkyl- or C₁₋₂alkyl-;
- R¹ represents hydrogen, halo or C₁₋₆alkyloxy-;
- R² represents hydrogen or halo;
- R³ represents hydrogen or cyano;
- R⁴ represents hydrogen or halo;
- 10 R⁵ represents hydrogen, halo or C₁₋₆alkyloxy-;
- R⁶ represents hydrogen;
- R⁷ represents hydrogen;
- R¹¹ represents hydrogen or C₁₋₄alkyl-;
- R¹⁶ and R¹⁸ represent hydrogen; and
- 15 R¹⁷ and R¹⁹ represent hydrogen;
- Het³ represents pyrrolidinyl.

- In a further object, the present invention provides the 4,6-pyrimidine derivatives of the
 20 formula (I) compounds, hereinafter referred to as the compounds of formula



- the *N*-oxide forms, the pharmaceutically acceptable addition salts and the
 stereochemically isomeric forms thereof, wherein Y, Z¹, Z², X¹, X², R¹, R², R³, R⁴ and
 R⁵ are defined as for the compounds of formula (I) hereinbefore, including any of the
 25 limitations as provided for the different groups of compounds of formula (I) as defined
 hereinbefore.

In particular those compounds of formula (I^b) wherein one or more of the following restrictions apply;

Z¹ and Z² represents NH;

Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₃₋₇alkyl-CO-NH- optionally substituted with

- 5 amino, mono- or di(C₁₋₄alkyl)amino or C₁₋₄alkyloxycarbonylamino-,
 -C₁₋₅alkyl-oxy-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-,
 -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-,
 -C₁₋₃alkyl-NH-CS-Het⁹-, -C₁₋₃alkyl-NH-CO-Het³-, C₁₋₂alkyl-CO-Het¹⁰-CO-,
 -Het⁴-CH₂-CO-NH-C₁₋₃alkyl-, -C₁₋₇alkyl-CO-, -C₁₋₆alkyl-CO-C₁₋₆alkyl-,
 10 -C₁₋₂alkyl-NH-CO-L¹-NH-, -C₁₋₂alkyl-CO-NH-L³-CO-, -CO-NH-L²-CO-,
 -C₁₋₂alkyl-NH-CO-L¹-NH-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-CO-,
 -C₁₋₂alkyl-CO-NR¹⁰-C₁₋₃alkyl-CO-, -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-,
 -NR¹²-CO-C₁₋₃alkyl-NH-, Het⁵-CO-C₁₋₂alkyl-, -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-,
 -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-, -Het⁶-CO-Het⁷-, -Het⁸-NH-C₁₋₃alkyl-CO-NH-,
 15 C₁₋₃alkyl-NH-CO-Het³²-CO-, or C₁₋₃alkyl-CO-Het³³-CO-NH-;

X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-, NR¹⁶,
 -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 in particular X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-,
 NR¹⁶, -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or
 20 -C₁₋₂alkyl-;

X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-, NR¹⁸,
 -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-, -Het²⁴-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 in particular X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-,
 NR¹⁸, -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-, -Het²⁴-C₁₋₂alkyl-, -O-N=CH- or
 25 -C₁₋₂alkyl-;

R¹ represents hydrogen, halo, C₁₋₆alkoxy-, Het²⁰ or R¹ represents
 C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-; in particular R¹ represents
 hydrogen halo or C₁₋₄alkyloxy-;

R² represents hydrogen, halo or hydroxy; in particular R² represents hydrogen or halo;

30 R³ represents hydrogen, nitro or cyano; in particular R³ represents hydrogen or cyano;

R⁴ represents hydrogen or halo;

R⁵ represents hydrogen, halo, C₁₋₆alkoxy-, Het²¹ or R⁵ represents

C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-; in particular R⁵ represents
 hydrogen, halo or C₁₋₆alkyloxy-;

35 R⁶ represents hydrogen;

R⁷ represents hydrogen, C₁₋₄alkyl, or Het¹³-C₁₋₄alkyl-; in particular R⁷ represents
 hydrogen or Het¹³-C₁₋₄alkyl-;

- R⁸ and R⁹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or di(C₁₋₄alkyl)-amino- or imidazolyl; in particular R⁷ represents hydrogen, C₁₋₄alkyl, or Het¹³-C₁₋₄alkyl-; even more particular R⁷ represents hydrogen or Het¹³-C₁₋₄alkyl-;
- 5 R¹⁰, R¹² and R¹³ each independently represent hydrogen or C₁₋₄alkyl optionally substituted with hydroxy or C₁₋₄alkyloxy; in particular R¹³ represents hydrogen, or C₁₋₄alkyl;
- R¹¹ represents hydrogen, or C₁₋₄alkyl;
- R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl,
- 10 C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- R¹⁷ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, Het¹⁴, Het¹⁵-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- L¹ represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol,
- 15 thiazolyl, cyano, hydroxyphenyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, C₁₋₄alkyloxyphenyl-, aminocarbonyl, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amine-, or imidazolyl; in particular L¹ represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, pyridinyl, methylsulfide, hydroxy, thiol, thiazolyl, cyano, hydroxyphenyl, polyhaloC₁₋₄alkyl-
- 20 phenyl-, C₁₋₄alkyloxy-, C₁₋₄alkyloxyphenyl-, aminocarbonyl, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amine-, or imidazolyl; more in particular L¹ represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or di(C₁₋₄alkyl)-amino- or imidazolyl;
- L² represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol,
- 25 thiazolyl, cyano, hydroxyphenyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, C₁₋₄alkyloxyphenyl-, aminocarbonyl, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amine-, or imidazolyl; in particular L² represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, thienyl, methylsulfide, hydroxy, or mono- or di(C₁₋₄alkyl)-amino-; more in particular L²
- 30 represents C₁₋₈alkyl optionally substituted with mono- or di(C₁₋₄alkyl)-amino-;
- L³ represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol,
- 35 thiazolyl, cyano, hydroxyphenyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, C₁₋₄alkyloxyphenyl-, aminocarbonyl, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amine-, or imidazolyl; in particular L³ represents C₁₋₈alkyl optionally

- substituted one or where possible two or more substituents selected from phenyl, pyridinyl, methylsulfide-, cyano, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, aminocarbonyl-, mono- or di(C₁₋₄alkyl)-amino-, C₃₋₆cycloalkyl, thiazolyl or thienyl; more in particular L³ represents C₁₋₈alkyl optionally substituted with
- 5 mono- or di(C₁₋₄alkyl)-amino-;
- Het¹ and Het² each independently represent morpholinyl pyridinyl, wherein said Het¹ or Het² are optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-; in particular Het¹ and Het² each independently represent
- 10 morpholinyl;
- Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or where possible two or more hydroxy or Het²²-carbonyl- substituents; in particular
- 15 Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or where possible two or more hydroxy substituents;
- Het⁵ and Het⁶ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁵ and Het⁶ are
- 20 optionally substituted with one or where possible two or more hydroxy substituents;
- Het⁷ and Het⁸ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁷ and Het⁸ are
- 25 optionally substituted with one or where possible two or more hydroxy substituents;
- Het⁹ and Het¹⁰ each independently represent a heterocycle selected from pyrrolidinyl, pyrrolyl, azetidiny, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁹ and Het¹⁰ are optionally substituted with one or where possible two or more
- 30 hydroxy or C₁₋₄alkyl substituents;
- Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 35 Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible

two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
Het¹³ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said
pyrrolidinyl or piperidinyl are optionally substituted with one or where possible
5 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said
pyrrolidinyl or piperidinyl are optionally substituted with one or where possible
two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
10 hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or
piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible
two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
15 Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said
Het¹⁶ is optionally substituted with one or where possible two or more substituents
selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl
or polyhydroxy-C₁₋₄alkyl-;
Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or
20 piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible
two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
Het²⁰ and Het²¹ each independently represent morpholinyl or pyridinyl;
Het²² represents piperazinyl or piperidinyl optionally substituted with C₁₋₄alkyl or
25 hydroxy;
Het²³ and Het²⁴ each independently represent pyrrolidinyl, decahydroquinolinyl or
piperidinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where
possible two or more substituents selected from hydroxy, Het²²-carbonyl- or
C₁₋₄alkyl; in particular Het²³ and Het²⁴ each independently represent pyrrolidinyl,
30 decahydroquinolinyl or pyridinyl wherein said Het²³ or Het²⁴ is optionally
substituted with one or where possible two or more substituents selected from
hydroxy or C₁₋₄alkyl;
Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl,
pyrrolidinyl or piperidinyl.

A further group of compounds according to the present invention consists of those compounds of formula (I^b) wherein one or more of the following restrictions apply;

Z¹ and Z² represents NH;

Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-,

- 5 -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-, -C₁₋₂alkyl-CO-Het¹⁰-CO-, -C₁₋₃alkyl-NH-CO-Het³-, -Het⁴-C₁₋₃alkyl-CO-NH-C₁₋₃alkyl-,
 -C₁₋₂alkyl-NH-CO-L¹-NH-, -NH-CO-L²-NH-, -C₁₋₂alkyl-CO-NH-L³-CO-,
 -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-, -C₁₋₂alkyl-CO-NH-L³-CO-NH-C₁₋₃alkyl-,
 -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-, Het⁵-CO-C₁₋₂alkyl-,
 10 -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-, -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-,
 -C₁₋₃alkyl-NH-CO-Het³²-CO-, or
 -C₁₋₃alkyl-CO-Het³³-CO-NH-; in particular Y represents -C₃₋₉alkyl-,
 -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-,
 -C₁₋₆alkyl-NH-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-, Het⁵-CO-C₁₋₂alkyl-, or
 15 -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-;

X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁶-C₁₋₂alkyl-,
 -CO-NR¹⁷-, Het²³-C₁₋₂alkyl- or C₁₋₂alkyl; in particular X¹ represents a direct bond,
 O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷- or C₁₋₂alkyl;

- X² represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl-,
 20 -CO-NR¹⁹-, Het²⁴-C₁₋₂alkyl- or C₁₋₂alkyl; in particular X² represents a direct bond,
 O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹- or C₁₋₂alkyl;

R¹ represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het¹ or
 C₁₋₄alkyloxy-;

R² represents hydrogen or halo;

- 25 R³ represents hydrogen or cyano;

R⁴ represents hydrogen or halo;

R⁵ represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het² or
 C₁₋₄alkyloxy-;

R⁶ represents hydrogen;

- 30 R⁷ represents hydrogen;

R¹¹ represents hydrogen or C₁₋₄alkyl;

R¹³ represents hydrogen;

R¹⁶ and R¹⁸ represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl-; in particular R¹⁶ and R¹⁸
 represent hydrogen;

- 35 R¹⁷ and R¹⁹ represent hydrogen;

L¹ represents C₁₋₈alkyl optionally substituted with one or where possible two or more
 substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-,

- C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl; in particular L¹ represents C₁₋₈alkyl;
- L² represents C₁₋₈alkyl optionally substituted with one or where possible two or more substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-,
5 C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;
- L³ represents C₁₋₈alkyl optionally substituted with one or where possible two or more substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;
- Het¹ represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het¹
10 represents morpholinyl or piperazinyl; more in particular Het¹ represents morpholinyl;
- Het² represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het² represents morpholinyl or piperazinyl; more in particular Het² represents morpholinyl;
- 15 Het³ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl; in particular Het³ represents piperazinyl, piperidinyl or pyrrolidinyl;
- Het⁴ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl; in particular Het⁴ represents piperazinyl or piperidinyl;
- Het⁵ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl, in particular Het⁵
20 represents piperazinyl or piperidinyl, more in particular Het⁵ represents piperazinyl;
- Het¹⁰ represents piperazinyl, piperidinyl, pyrrolidinyl or azetidiny; in particular Het¹⁰ represents pyrrolidinyl, piperazinyl or azetidiny, more in particular Het¹⁰ represents azetidiny;
- 25 Het¹⁷ represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl; in particular Het¹⁷ represents morpholinyl or piperazinyl;
- Het²² represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl wherein said Het²² is optionally substituted with C₁₋₄alkyl; in particular Het²² represents morpholinyl or piperazinyl wherein said morpholinyl or piperazinyl or optionally substituted with
30 C₁₋₄alkyl; more in particular Het²² represents piperazinyl optionally substituted with C₁₋₄alkyl;
- Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ are optionally substituted with Het²²-carbonyl;
- 35 Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl, in particular Het³² and Het³³ are each independently selected from morpholinyl, piperazinyl or piperidinyl, more in

particular Het³² and Het³³ are each independently selected from morpholinyl or piperidinyl;

- A further group of compounds according to the present invention consists of those compounds of formula (I) wherein one or more of the following restrictions apply;
- 5 Z^1 and Z^2 represents NH;
- Y represents -C₃₋₉alkyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-NH-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-, Het⁵-CO-C₁₋₂alkyl-, NH-CO-L²-NH- or -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-; in particular Y
- 10 represents -C₃₋₉alkyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-NH-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH- or -NH-CO-L²-NH-;
- X¹ represents O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl- or Het²³-C₁₋₂alkyl-; in particular X¹ represents O, -O-C₁₋₂alkyl- or -CO-C₁₋₂alkyl-;
- X² represents O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl- or Het²⁴-C₁₋₂alkyl-; in particular X²
- 15 represents O, -O-C₁₋₂alkyl- or -CO-C₁₋₂alkyl-;
- R¹ represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het¹;
- R² represents hydrogen or halo;
- R³ represents hydrogen or cyano;
- R⁴ represents hydrogen or halo;
- 20 R⁵ represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het²;
- R⁶ represents hydrogen;
- R⁷ represents hydrogen;
- R¹¹ represents hydrogen or C₁₋₄alkyl;
- R¹³ represents hydrogen;
- 25 L¹ represents C₁₋₈alkyl optionally substituted with one or where possible two or more substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl; in particular L¹ represents C₁₋₈alkyl;
- L² represents C₁₋₈alkyl optionally substituted with one or where possible two or more
- 30 substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl; in particular L² represents C₁₋₈alkyl;
- Het¹ represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het¹ represents morpholinyl or piperazinyl; more in particular Het¹ represents
- 35 morpholinyl;

Het² represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het² represents morpholinyl or piperazinyl; more in particular Het² represents morpholinyl;

5 Het⁵ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl, in particular Het⁵ represents piperazinyl or piperidinyl, more in particular Het⁵ represents piperazinyl;

10 Het²² represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl wherein said Het²² is optionally substituted with C₁₋₄alkyl; in particular Het²² represents morpholinyl or piperazinyl wherein said morpholinyl or piperazinyl or optionally substituted with C₁₋₄alkyl; more in particular Het²² represents piperazinyl optionally substituted with C₁₋₄alkyl;

Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ are optionally substituted with Het²²-carbonyl; in particular Het²³ and Het²⁴ represent pyrrolidinyl.

15

In a further embodiment of the present invention the compounds of formula (I) are selected from the group consisting of;

1H,7H-6,2:12,8-dimetheno-13,1,3,5,7,16,19-benzoxahexaazacyclotricosine-17,20(14H)-dione, 24-chloro-15,16,18,19,21-pentahydro-11-methoxy-

6,2:12,8-dimetheno-7H-13,1,3,5,7,17,20-benzoxahexaazacyclotetracosine-18,21-dione, 25-chloro-1,14,15,16,17,19,20,22-octahydro-11-methoxy-19-(2-methylpropyl)-, (19S)-

1H,7H-2,6:12,8-dimetheno-13,20,1,3,5,7-benzodioxatetraazacyclodocosine, 23-bromo-14,15,16,17,18,19-hexahydro-11-methoxy-

1H,7H-6,2:8,12-dimetheno-13,20,1,3,5,7-benzodioxatetraazacyclodocosine, 23-bromo-14,15,16,17,18,19-hexahydro-10-methoxy-

1H,7H-2,6:12,8-dimetheno-14H-13,19,1,3,5,7-benzodioxatetraazacycloheneicosine, 22-bromo-15,16,17,18-tetrahydro-11-methoxy-

1H,7H-6,2:8,12-dimetheno-13,20,1,3,5,7,17-benzodioxapentaazacyclodocosine, 23-chloro-14,15,16,17,18,19-hexahydro-11-methoxy-

6,2:8,12-dimetheno-7H-13,1,3,5,7,17,20-benzoxahexaazacyclotetracosine-18,21-dione, 25-chloro-1,14,15,16,17,19,20,22-octahydro-11-methoxy-19,19-dimethyl-

1H,7H-6,2:8,12-dimetheno-13,1,3,5,7,16,19-benzoxahexaazacyclotricosine-17,20(14H)-dione, 24-chloro-15,16,18,19,21-pentahydro-18,18-dimethyl-11-[3-(4-morpholinyl)propoxy]-

1H,7H-6,2:8,12-dimetheno-13,1,3,5,7,16,19-benzoxahexaazacyclotricosine-17,20(14H)-dione, 24-chloro-15,16,18,19,21-pentahydro-11-[3-(4-

morpholinyl)propoxy]-

- 14,21-dioxa-2,4,8,17,28-pentaazatetracyclo[20.3.1.1~3,7~.1~9,13~]octacos-
1(26),3,5,7(28),9,11,13(27),22,24-nonaene-6-carbonitrile, 16-oxo-
- 14,19-dioxa-2,4,8,26-tetraazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacos-
1(24),3,5,7(26),9,11,13(25),20,22-nonaene-6-carbonitrile
- 14,21-dioxa-2,4,8,18,28-pentaazatetracyclo[20.3.1.1~3,7~.1~9,13~]octacos-
1(26),3,5,7(28),9,11,13(27),22,24-nonaen-19-one
- 21,17-metheno-15,11-nitrilo-16H-pyrrolo[2,1-
r][13,1,5,7,16,19]benzoxapentaazacyclodocosine-12-carbonitrile, 8-chloro-7-
fluoro-1,2,3,5,10,23,24,25,26,26a-decahydro-20-methoxy-26-oxo-, (26aS)-
- 14,22-dioxa-2,4,8,19,29-pentaazatetracyclo[21.3.1.1~3,7~.1~9,13~]nonacos-
1(27),3,5,7(29),9,11,13(28),23,25-nonaen-20-one
- 12,8-metheno-6,2-nitrilo-7H-13,1,5,7,16,19-benzoxapentaazacyclodocosine-3-
carbonitrile, 23-chloro-1,14,15,16,17,18,19,20-octahydro-11-methoxy-19-
methyl-17-oxo-
- 1H,7H-12,8-metheno-6,2-nitrilo-13,1,5,7,17,20-benzoxapentaazacyclotricosine-3-
carbonitrile, 24-chloro-14,15,16,17,18,19,20,21-octahydro-11-methoxy-20-
methyl-18-oxo-

Other special group of compounds are:

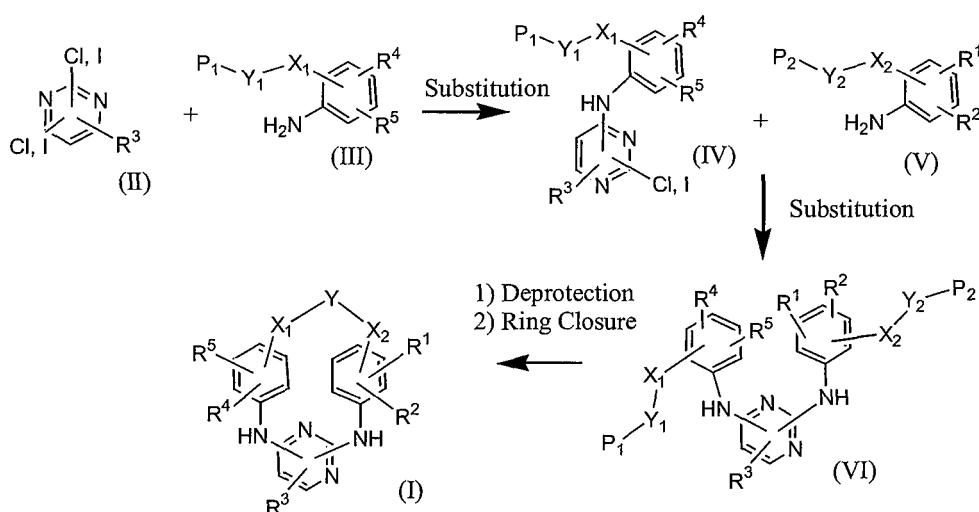
- those compounds of formula (I) wherein $-X^1$ - or $-X^2$ represents $-O$ -;
- 5 - those compounds of formula (I) wherein $-X^1$ - represents $-C_{1-2}alkyl-NR^{16}$ -;
- those compounds of formula (I) wherein $-X^2$ - represents $-C_{1-2}alkyl-NR^{17}$ -;
- those compounds of formula (I) wherein $-X^1$ - represents either of a direct bond, $-O$ -, $-O-C_{1-2}alkyl$ - or $-NR^{16}-C_{1-2}alkyl$ - and wherein $-X^2$ - represents either of $-O$ -, $-O-C_{1-2}alkyl$ -, $-NR^{17}-C_{1-2}alkyl$ or $-Het^{24}-C_{1-2}alkyl$ -;
- 10 - those compounds of formula (I) wherein $-X^1$ - represents $-O$ - or $-NR^{16}-C_{1-2}alkyl$ - and wherein $-X^2$ - represents $-NR^{17}-C_{1-2}alkyl$ or $-Het^{24}-C_{1-2}alkyl$ -;
- those compounds of formula (I) wherein $-X^1$ - represents $-CO-NR^{17}$ -, in particular $CO-NH$;
- those compounds of formula (I) wherein $-X^2$ - represents $-CO-NR^{18}$ -, in particular
- 15 $CO-NH$;
- those compounds of formula (I) wherein R^1 represent fluor and R^2 represents Cl;
- those compounds of formula (I) wherein R^2 represents Cl;
- those compounds of formula (I) wherein R^2 represents hydrogen;
- those compounds of formula (I) wherein R^1 represents chloro or fluoro;
- 20 - those compounds of formula (I) wherein R^5 represents hydrogen or $C_{1-4}alkyloxy$ -;

- those compounds of formula (I) wherein R⁵ represents C₁₋₄alkyloxy-, in particular methoxy;
- those compounds of formula (I) wherein R⁴ represents hydrogen;
- those compounds of formula (I) wherein Y represents C₃₋₉alkyl and R¹ and R² each independently represent -O- or CO-NH;
- those compounds of formula (I) wherein Y represents -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl, -C₁₋₂alkyl-NH-CO-L¹-NH-, -C₁₋₂alkyl-CO-NH-L³-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-, -C₁₋₂alkyl-CO-NH-L³-CO-NH-, -C₁₋₂alkyl-CO-NH-L³-CO-NH-C₁₋₃alkyl-, -CO-NH-L²-CO- or -NH-CO-L²-NH-;
- those compounds of formula (I) wherein Y represents -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl, -C₁₋₂alkyl-CO-NH-L³-CO-, -C₁₋₂alkyl-CO-NH-L³-CO-NH-C₁₋₃alkyl-, -C₁₋₃alkyl-CO-Het²⁸-CO-NH-, -C₁₋₆alkyl-CO-NH-, -C₁₋₂alkyl-CO-Het¹⁰-CO-, -C₁₋₃alkyl-NH-CO-Het²⁷-CO- or -Het⁴-C₁₋₃alkyl-CO-NH-C₁₋₃alkyl-;
- those compounds of formula (I) wherein Y represents -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl, -C₁₋₂alkyl-NH-CO-L¹-NH-, -C₁₋₂alkyl-CO-NH-L³-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-, -C₁₋₂alkyl-CO-NH-L³-CO-NH-, -C₁₋₂alkyl-CO-NH-L³-CO-NH-C₁₋₃alkyl-, -CO-NH-L²-CO-, -NH-CO-L²-NH-, -C₁₋₃alkyl-CO-Het²⁸-CO-NH-, -C₁₋₆alkyl-CO-NH-, -C₁₋₂alkyl-CO-Het¹⁰-CO-, -C₁₋₃alkyl-NH-CO-Het²⁷-CO- or -Het⁴-C₁₋₃alkyl-CO-NH-C₁₋₃alkyl-;

In a further embodiment of the present invention the X² substituent is at position 3', the R¹ substituent represents hydrogen or halo and is at position 4', the R² substituent represents halo and is at position 5', the X¹ substituent is at position 3', the R⁵ substituent is at position 4' and represents hydrogen or C₁₋₄alkyloxy- and the R⁴ substituent at position 5' of the structure of formula (I). Alternatively, the X² substituent is at position 2', the R¹ substituent represents hydrogen or halo and is at position 4', the R² substituent represents halo and is at position 5', the X¹ substituent is at position 3', the R⁵ substituent is at position 4' and represents hydrogen or C₁₋₄alkyloxy- and the R⁴ substituent at position 5' of the structure of formula (I).

The compounds of this invention can be prepared by any of several standard synthetic processes commonly used by those skilled in the art of organic chemistry and include both solution phase and solid phase chemistry techniques. These standard synthetic processes are for example described in the following references; "Heterocyclic Compounds" – Vol.24 (part4) p 261-304 Fused pyrimidines, Wiley – Interscience ;

Chem. Pharm. Bull., Vol 41(2) 362-368 (1993); J.Chem.Soc., Perkin Trans. 1, 2001, 130-137. In brief, in a first step a 2,4 or 4,6-di-I or di-Cl-pyrimidine (II) is aminated with an appropriate aniline of formula (III) to yield the anilinopyrimidine of general formula (IV). In a second step this anilinopyrimidine is further substituted with a further aniline of general formula (V) which provides the bis(aniline)pyrimidines of formula (VI). Deprotection and ring closure provides the compounds of the present invention.



- 10 Wherein Y₁ and Y₂ each independently represent C₁₋₇alkyl, C₃₋₇alkenyl or C₃₋₇alkynyl wherein said C₁₋₇alkyl, C₃₋₇alkenyl, C₃₋₇alkynyl are optionally substituted with one or where possible two or more substituents selected from amino, mono- or di(C₁₋₄alkyl)amino, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfonyl and C₁₋₄alkyloxycarbonylamino; or Y₁ and Y₂ each independently represent Het', Het'-CO,
- 15 Het'-C₁₋₅alkyl, CR⁸R⁹-NH, CR⁸R⁹-NH-CO, CR²⁰R²¹-CO, CR²⁰R²¹-CO-NH, CO-C₁₋₃alkyl, NH-CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂, CH₂-CO-NH-C₁₋₃alkyl or C₁₋₃alkyl-NH, wherein R⁸, R⁹, R¹¹, R²⁰ and R²¹ are as defined for the compounds of formula (I) hereinbefore and wherein Het' represents a heterocycle selected from the group consisting of pyrrolidinyl, 2-pyrrolidinyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het' is
- 20 optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl, wherein Het²² is as defined for the compounds of formula (I).

P₁ and P₂ each independently represent optionally protected functional groups, such as for example a primary or secondary amine, hydroxy, hydroxycarbonyl or halo (Cl, Br or I), which

25 upon reaction produce together with the Y₁ respectively Y₂ substituent to which they are attached, the divalent Y radical as defined for the compounds of formula (I) hereinbefore.

The aniline derivatives of formula (III) or (V) are either known structures or obtained using standard synthetic processes commonly used by those skilled in the art of organic chemistry, in particular departing from suitable nitrobenzaldehydes or nitrophenols. See for example the general synthesis schemes 6-12 hereinafter.

5

In case of solid phase chemistry the compounds of the present invention are generally prepared according to Scheme 1.

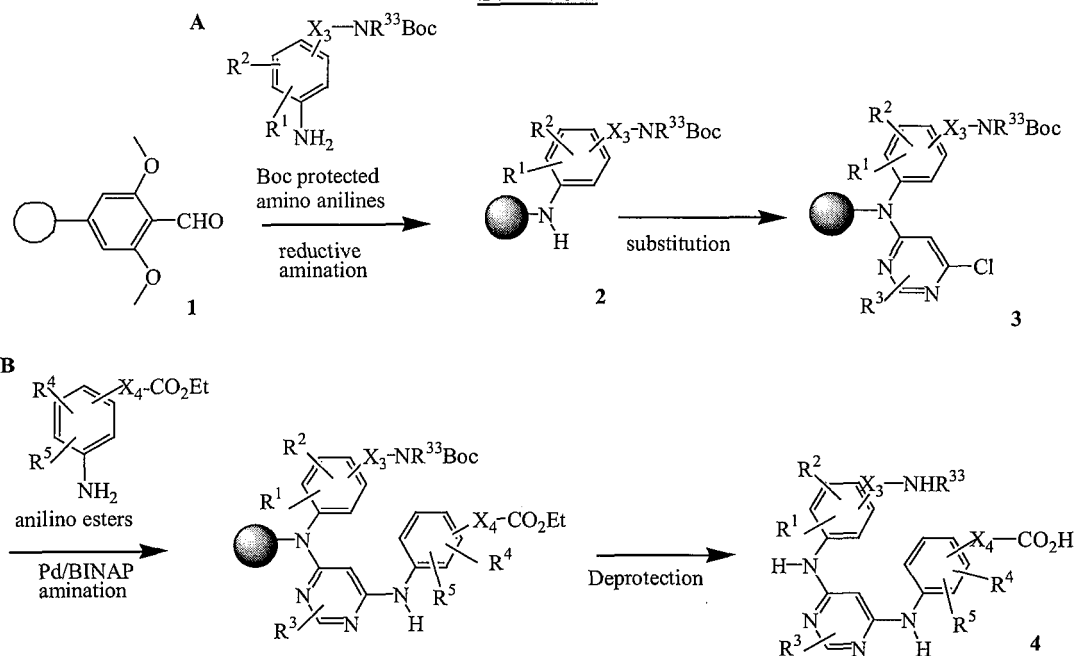
10 In a first step, a formyl functionalized polystyrene such as for example 2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene (**1**) is aminated with an appropriate Boc-protected amino aniline of formula (**A**) by reductive amination using art known conditions, such as for example using NaBH₄ and titanium(IV)isopropoxide as reducing agents in CH₂Cl₂/CH₃COOH 1% or DMF/ CH₃COOH 1% as solvent. This reaction is typically performed overnight at room temperature.

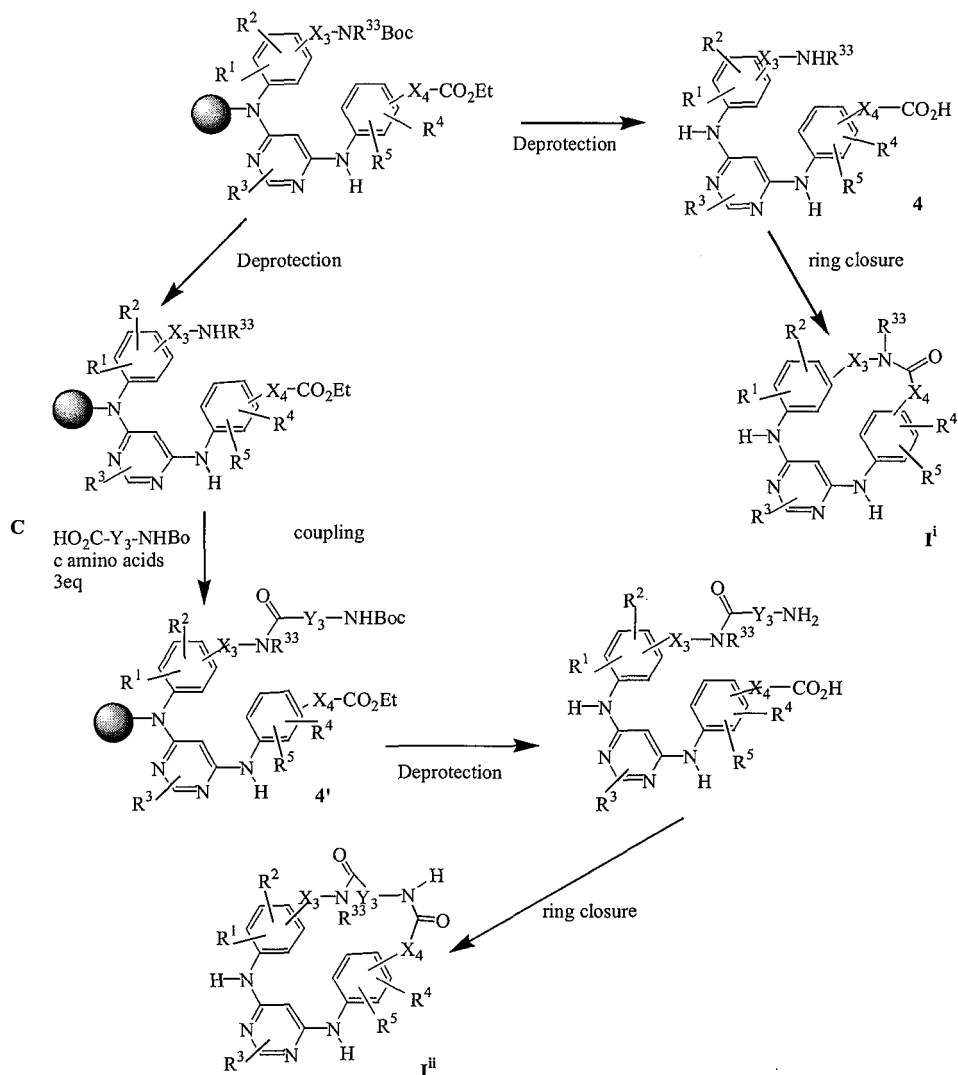
15 The thus obtained secondary amine (**2**) is subsequently coupled to 2,4 or 4,6-di-I or di-Cl-pyrimidine by stirring the reagents in an appropriate solvent such as propanol or 1-butanol at an elevated temperature (at 60-90°C) for about 40 hours in the presence of *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (DIPEA).

To obtain the bis(anilino)pyrimidine scaffold of the present invention, the intermediate resin (**3**) is further reacted with an appropriate aniline ester (**B**) using the Pd/BINAP catalyzed amination reaction, i.e. typically performed in toluene or dioxane as a solvent, using Pd₂(dba)₃ or Pd(OAc)₂ as precatalyst at a ratio of BINAP to Pd in the range of 5.0 – 1.0, optionally in the presence of a weak base such as for example Cs₂CO₃. This reaction is performed under N₂ and shaken for 10-20 h at a temperature
25 ranging from 65 to 110°C.

Deprotection provides the intermediates **4** or **4'** which after ring closure provides the compounds of formula Iⁱ or are further elongated with Boc-protected amino acids (C) to yield the compounds of formula Iⁱⁱ.

Scheme 1

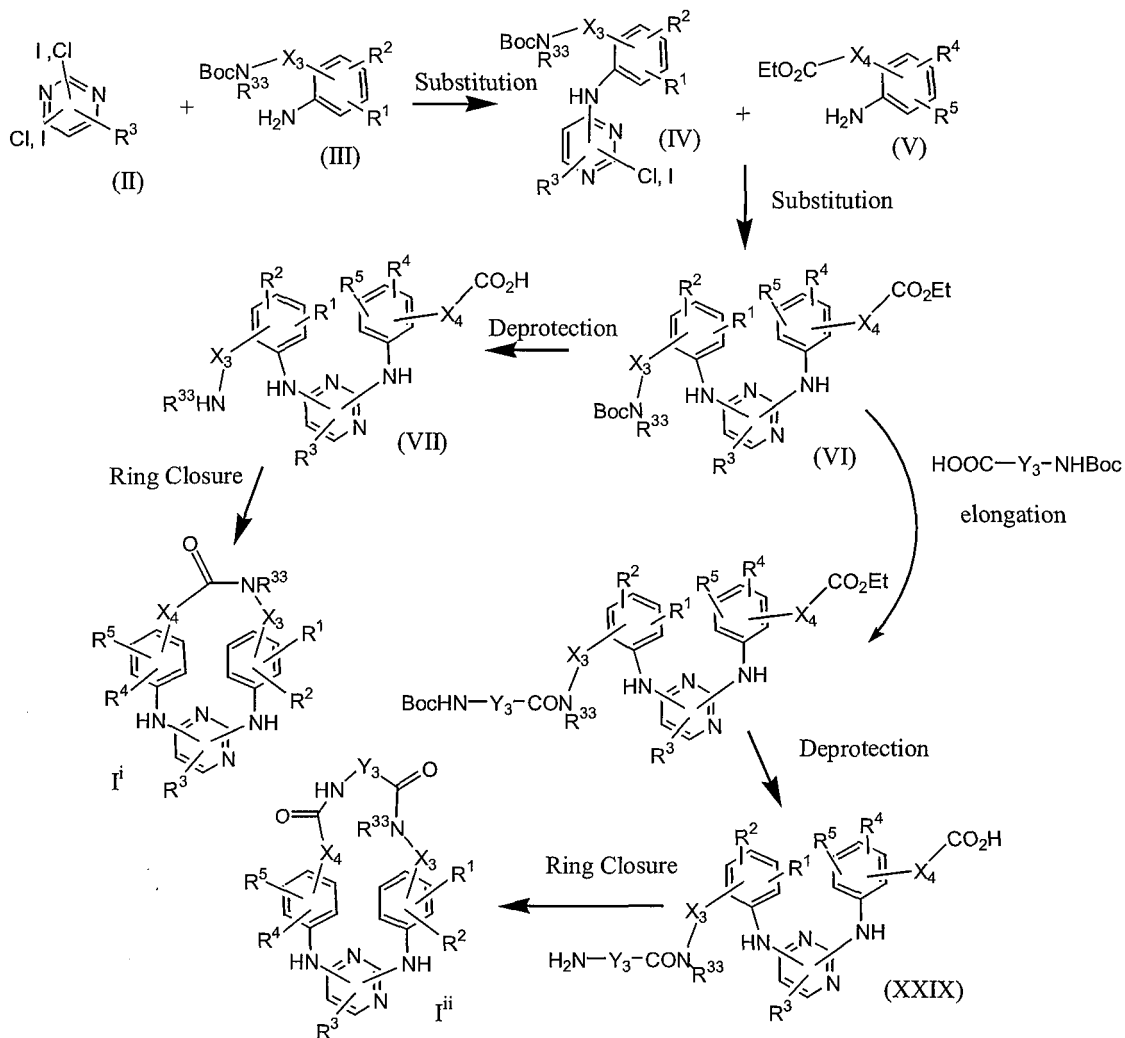




- Wherein X_3 and X_4 each independently represent a direct bond, C_{1-7} alkenyl, C_{3-7} alkynyl, C_{1-5} alkyl- O - C_{1-5} alkyl, C_{1-5} alkyl- NR^{30} - C_{1-5} alkyl, C_{1-2} alkyl- CO -Het¹⁰, Het²³, O - C_{1-2} alkyl or CR^8R^9 ; wherein Het¹⁰, Het²³ R^8 and R^9 are defined as for the compounds of formula (I). Wherein Y_3 represents Het⁶- CO -Het⁷, C_{1-6} alkyl, C_{1-6} alkyl- CO - NH - C_{1-6} alkyl or $CR^{31}R^{32}$; wherein R^{31} and R^{32} each independently represent hydrogen or C_{1-4} alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxyl, thiol, hydroxyphenyl, C_{1-4} alkyloxyphenyl, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C_{1-4} alkyl)amine, imidazolyl or guanidino; and wherein Het⁶ and Het⁷ are defined as for the compounds of formula (I). Wherein R^{30} represents hydrogen, C_{1-4} alkyl, Het¹¹, Het¹²- C_{1-4} alkyl, phenyl- C_{1-4} alkyl, phenyl or mono- or di(C_{1-4} alkyl)amino- C_{1-4} alkyl-carbonyl wherein said R^{30} is optionally substituted with hydroxy, amino, mono- or di(C_{1-4} alkyl)amino, pyrimidinyl or C_{1-4} alkyloxy. Wherein R^{33} represents hydrogen, C_{1-4} alkyl, Het¹⁴ or C_{1-4} alkyl substituted with one or where possible two or more substituents selected from hydroxy, amino, mono- or di(C_{1-4} alkyl)amino, phenyl, Het¹⁵ or C_{1-2} alkyloxy and wherein $\bullet$ represents 2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene (1).

In case of solution phase chemistry the compounds of the present invention are generally prepared according to reaction scheme 2.

Scheme 2



- 5 Wherein X₃ and X₄ each independently represent a direct bond, C₁₋₇alkyl, C₃₋₇alkenyl, C₃₋₇alkynyl, C₁₋₅alkyl-O-C₁₋₅alkyl, C₁₋₅alkyl-NR³⁰-C₁₋₅alkyl, C₁₋₂alkyl-CO-Het¹⁰, Het²³, O-C₁₋₂alkyl or CR⁸R⁹; wherein Het¹⁰, Het²³, R⁸ and R⁹ are defined as for the compounds of formula (I). Wherein Y₃ represents Het⁶-CO-Het⁷, C₁₋₆alkyl, C₁₋₆alkyl-CO-NH-C₁₋₆alkyl or CR³¹R³²; wherein R³¹ and R³² each independently represent hydrogen or C₁₋₄alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxyl, thiol, hydroxyphenyl, C₁₋₄alkyloxyphenyl, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)amine, imidazolyl or guanidino; and wherein Het⁶ and Het⁷ are defined as for the compounds of formula (I). Wherein R³⁰ represents hydrogen, C₁₋₄alkyl, Het¹¹, Het¹²-C₁₋₄alkyl, phenyl-C₁₋₄alkyl, phenyl or mono- or di(C₁₋₄alkyl)amino-C₁₋₄alkyl-carbonyl wherein said R³⁰ is optionally substituted with hydroxy, amino, mono- or di(C₁₋₄alkyl)amino, pyrimidinyl or C₁₋₄alkyloxy. Wherein R³³ represents hydrogen, C₁₋₄alkyl, Het¹⁴ or C₁₋₄alkyl substituted with one or where possible two or more substituents selected from hydroxy, amino, mono- or di(C₁₋₄alkyl)amino, phenyl, Het¹⁵ or C₁₋₂alkyloxy.
- 10
- 15

In a first substitution reaction a Boc-protected amino aniline (III) is coupled to 2,4 or 4,6-di-I or di-Cl-pyrimidine (II) by stirring for example the reagents in an appropriate solvent such as propanol or 1-butanol at an elevated temperature (at 60-90°C) for about 40 hours in the presence of *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (DIPEA),
5 yielding the anilinopyrimidines of general formula IV. In a second substitution reaction under comparable reaction conditions, said intermediate (IV) is coupled to the aniline ester of general formula (V) yielding the bis(anilino)pyrimidine of formula (VI). Deprotection provides the intermediates of formula VII which after ring closure provides the compounds of formula Iⁱ. Further elongation of the amine in VII with
10 Boc-protected amino acids under art known conditions, see for example the synthesis of intermediate 36 in example A10c, yields after deprotection and ring closure the compounds of formula Iⁱⁱ. Ring closure is typically performed in the presence of a coupling reagent such as for example 1,3-dicyclohexylcarbodiimide (DCC), *N,N'*-carbonyldiimidazole (CDI), POCl₃, TiCl₄, sulfur chloride fluoride (SO₂ClF) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) in the presence or absence of 1-hydroxybenzotriazole (HOBt).
15

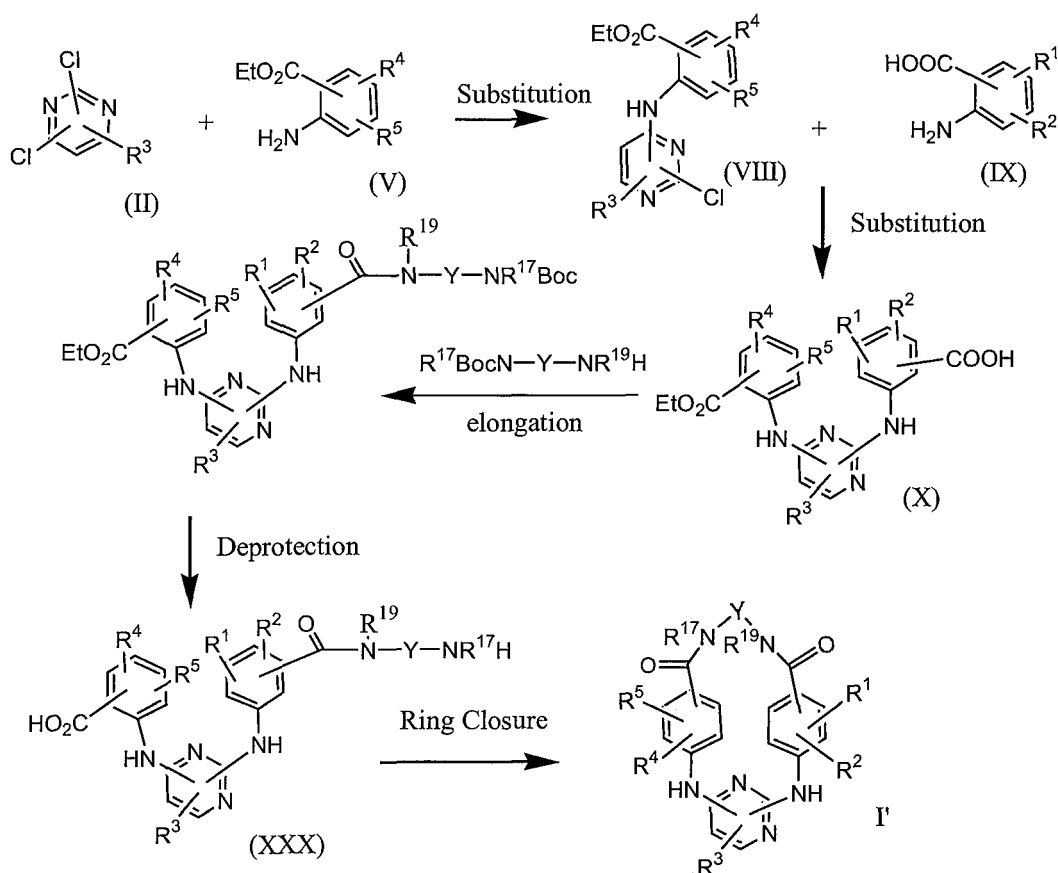
As further exemplified in the experimental part of the description, a particular group of compounds are those compounds of formula (I) where -X¹- and -X²- represent
20 -C=O-NR¹⁷- and -C=O-NR¹⁹- respectively, hereinafter referred to as compounds of formula (I') which are generally prepared using the following synthesis scheme (scheme 3).

As for the general synthesis scheme (Scheme 2) hereinbefore, in a first substitution
25 reaction an aniline ester (V) is coupled to the 2,4 or 4,6-di-I or di-Cl-pyrimidine by stirring for example the reagents in an appropriate solvent such as propanol or 1-butanol at an elevated temperature (at 60-90°C) for about 40 hours in the presence of *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (DIPEA), yielding the anilinopyrimidines of general formula VIII. In a second substitution reaction an amino benzoic acid (IX) was
30 coupled to the anilinopyrimidine of formula VIII under art known conditions, such as for example using hydrochloric acid (6N) in isopropanol as solvent and stirring for 1 – 3 h at an elevated temperature ranging from 110-170°C, to yield the bis(anilino)pyrimidines intermediates of formula X. To obtain the diamide- linker in the final compounds, said bis(anilino)pyrimidine is subsequently elongated by
35 amidation with an appropriate Boc-protected diamine using standard coupling reagents such as 1,3-dicyclohexylcarbodiimide (DCC), *N,N'*-carbonyldiimidazole (CDI), POCl₃, TiCl₄, sulfur chloride fluoride (SO₂ClF) or 1-(3-dimethylaminopropyl)-3-

ethylcarbodiimide (EDCI) in the presence or absence of 1-hydroxybenzotriazole (HOBt) Deprotection and ring closure by macrolactamization (see above) yields compounds according to the invention.

5

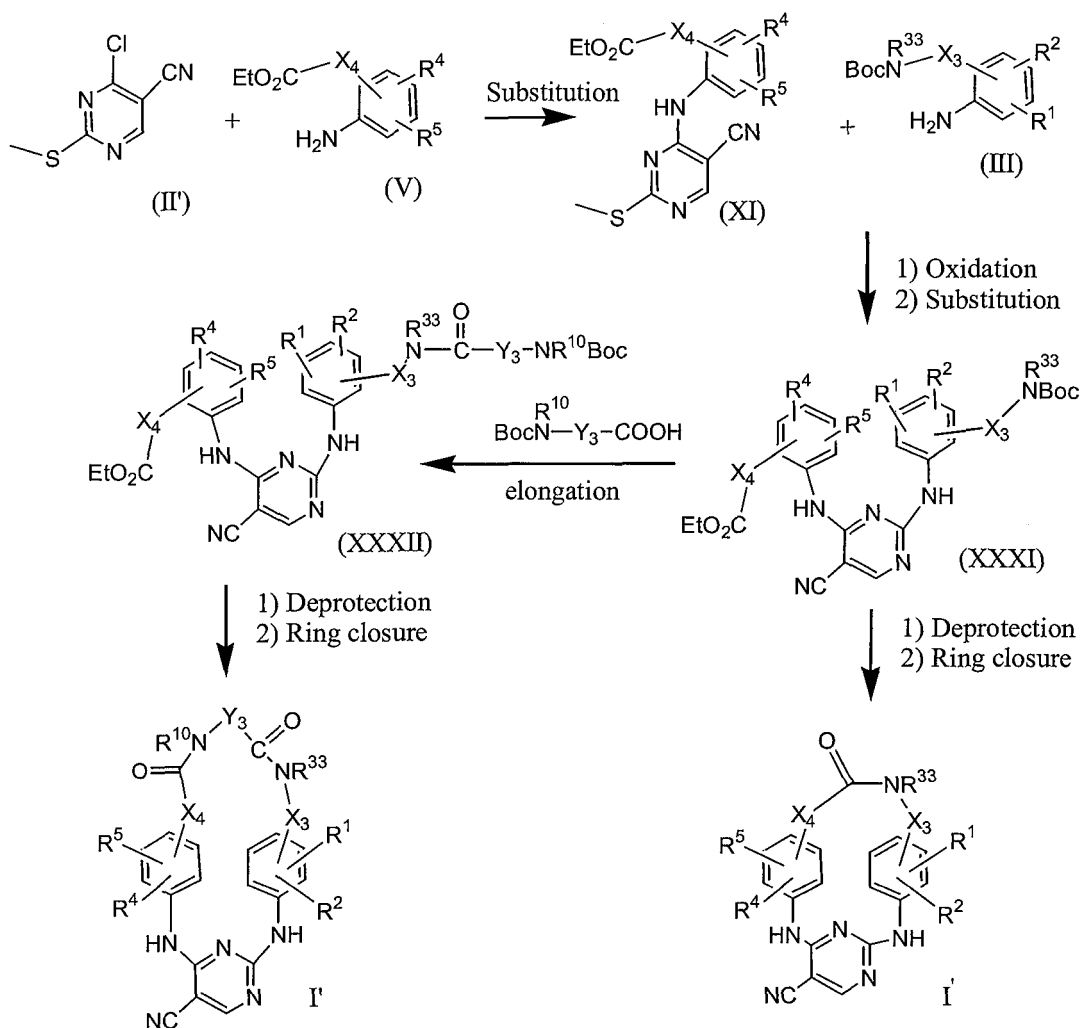
Scheme 3



Wherein Y, R¹, R², R³, R⁴, R⁵, R¹⁷ and R¹⁹ are defined as for the compounds of formula (I)

- 10 An alternative synthesis route for the compounds of the present invention, in particular for the 2,4-bis(aniline)-5-cyano-pyrimidine derivatives of formula I' supra, comprises the use of 4-chloro-2-(methylthio)pyrimidine-5-carbonitrile instead of 2,4-dichloro-pyrimidine-5-carbonitrile as building block (Scheme 4). This building block allows for selective introduction of one aniline in the 4-position. The second aniline can then be
- 15 introduced after oxidation of the sulfur atom. Because of the known sensitivity of the nitrile function towards hydrolysis, a tBu ester, which can be deprotected under anhydrous conditions, is preferred.

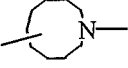
Scheme 4



Wherein X₃, X₄ and Y₃ are defined as for schemes 1&2 hereinbefore and wherein R¹, R², R⁴, R⁵ and R¹⁰ are defined as for the compounds of formula (I).

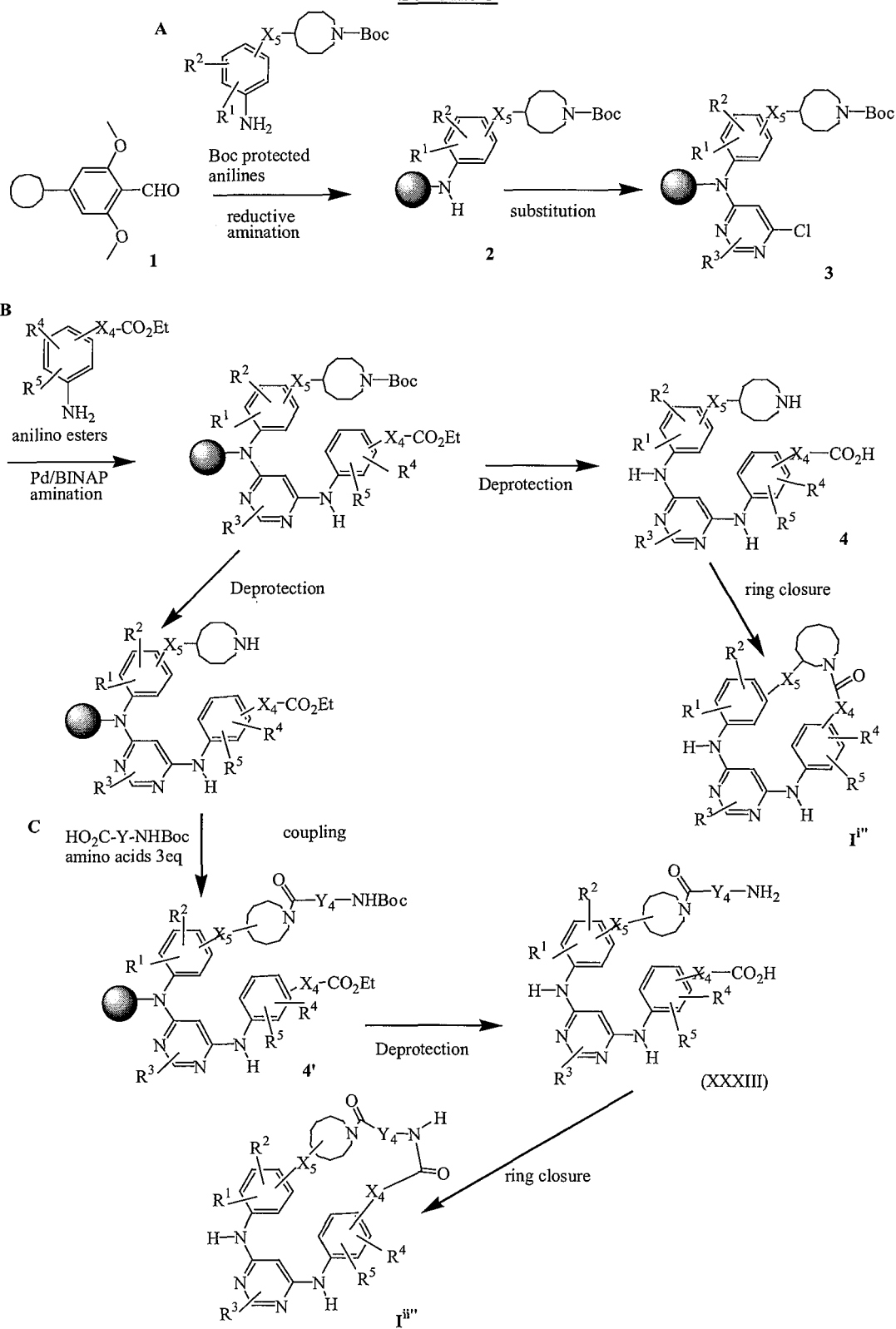
As for the general synthesis scheme (Scheme 2) hereinbefore, in a first substitution reaction an aniline ester (V) is coupled to the 4-chloro-2-methylsulfide-pyrimidine-5-carbonitrile (II') by stirring for example the reagents in an appropriate solvent such as propanol or 1-butanol at an elevated temperature (at 60-90°C) for about 40 hours in the presence of *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (DIPEA), yielding the anilinyrimidines of general formula XI. The second Boc-protected amino aniline (III) is introduced at the 2-position after oxidizing the sulphur atom of XI. This oxidation is typically performed with *m*-chloroperbenzoic acid in CH₂Cl₂ (DCM) or CH₂Cl-CH₂Cl (DCE) under art known conditions as exemplified in the synthesis examples hereinafter. Deprotection and ring closure by macrolactamization (see above) yields the compounds according to the invention.

For the synthesis of those compounds of formula (I) wherein Y represents Het⁵-CO-C₁₋₂alkyl or Het⁶-CO-Het⁷ hereinafter referred to as the compounds of formula I'', the following synthesis scheme is generally applied (Scheme 5). As used

5 herein,  represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinoyl, piperazinyl or piperidinyl optionally substituted with one or where possible two or more substituents selected from hydroxyl, C₁₋₄alkyl, hydroxyl-C₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl. X₅ and X₄ represent a direct bond, -O-, -O-C₁₋₆alkyl-, C₁₋₂alkyl, Het⁷-C₁₋₂alkyl-, C₁₋₄alkyl-NR¹⁶-C₁₋₂alkyl or C₁₋₂alkyl-Het⁷-C₁₋₂alkyl; Y₄ represents 10 C₁₋₆alkyl-, C₁₋₆alkyl-CO-NH-C₁₋₄alkyl or CR⁸R⁹; wherein Het⁷, R¹, R², R³, R⁴, R⁵, R⁸, R⁹ and R¹⁶ are defined as for the compounds of formula (I) and wherein  represents 2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene (1).

This reactions scheme only differs from the general solid phase reaction scheme 1 in 15 that in the first step, the formyl functionalized polystyrene such as for example 2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene (1) is aminated with an appropriate Boc-protected aniline of formula (A) by reductive amination. As for scheme 1, the next steps consist of a first coupling with the appropriate 2,4 or 4,6-di-I or di-Cl-pyrimidine followed by a substitution with the appropriate aniline ester (B) to 20 yield the bis(aniline)pyrimidine scaffold of the present invention. Deprotection and optional elongation, provides after ring closure the compounds of formula (I^{i''}) and (I^{ii''}) respectively.

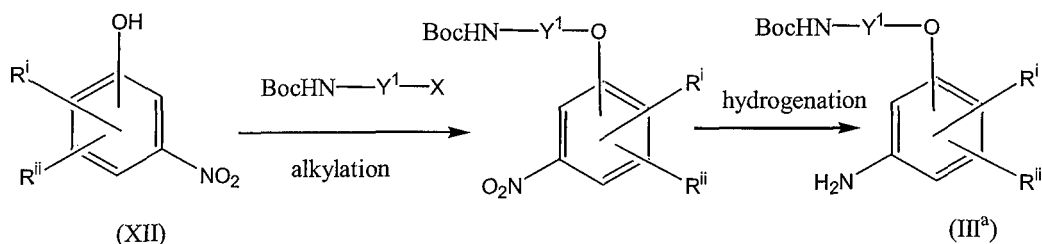
Scheme 5



For those compounds where X^1 or X^2 represents -O-, the suitable Boc-protected amino anilines (III^a) are generally prepared by alkylation from the known nitrophenols (XII), with a Boc-protected aminoalkylhalide followed by hydrogenolysis of the nitro group using art known procedures (Scheme 6).

5

Scheme 6

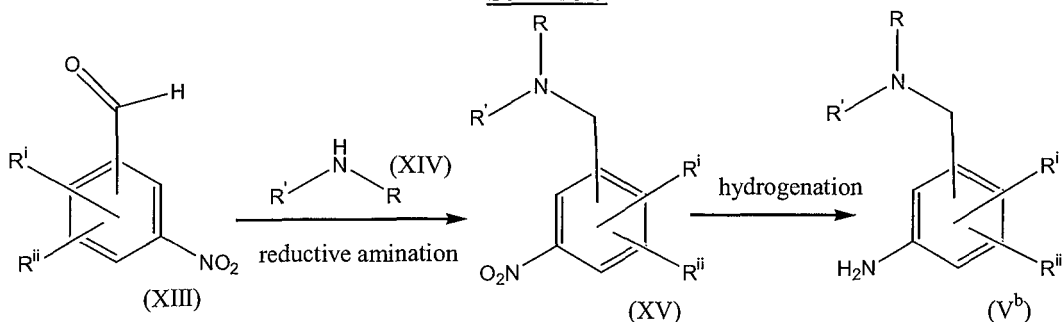


as used in scheme 6, R^i represents either R^1 or R^5 as defined for the compounds of formula(I) hereinbefore and R^{ii} represents either R^2 or R^4 as defined for the compounds of formula(I) hereinbefore.

For those compounds where X^1 or X^2 represents $NR^{12}-C_{1-2}alkyl-$, the suitable aniline esters of formula (V^b) are generally prepared from the known nitro-benzaldehydes (XIII) and an amine (XIV) by reductive amination under standard conditions (Scheme 7), for example using $NaBH_4$ and titanium(IV)isopropoxide as reducing agents in ethanol as solvent, yielding in a first step the nitro-benzylamines of formula (XV). Subsequent hydrogenolysis of the nitro group provides the intermediates of the present invention.

20

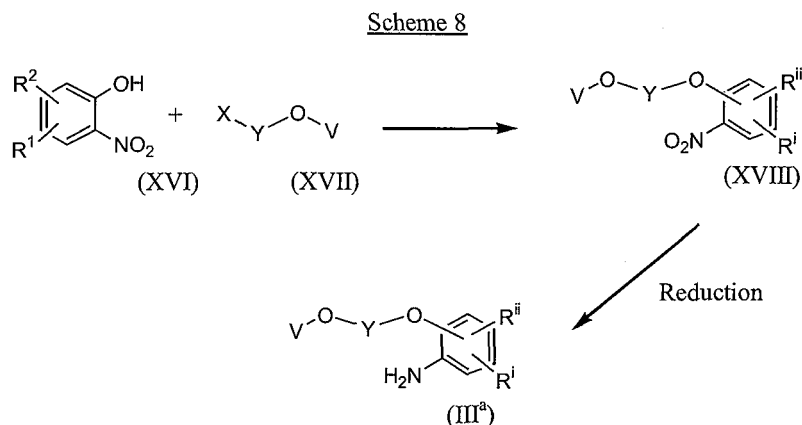
Scheme 7



as used in scheme 7, R^i represents either R^1 or R^5 as defined for the compounds of formula(I) hereinbefore and R^{ii} represents either R^2 or R^4 as defined for the compounds of formula(I) hereinbefore.

25

Alternatively for those compounds (I) where X^1 or X^2 represents -O-, the suitable substituted anilines of formula (III^a) are generally prepared from the commercially available nitro-phenols (XVI) and the α , ω -protected halogenated alcohols (XVII) under alkaline conditions in a reaction inert solvent, for example, using dimethylacetamide (DMA) in the presence of K_2CO_3 . The resulting nitro-phenyl derivative (XVIII) is subsequently reduced according to standard conditions, for example, using iron/acetic acid, to yield the substituted anilines of formula (III^a) (Scheme 8).

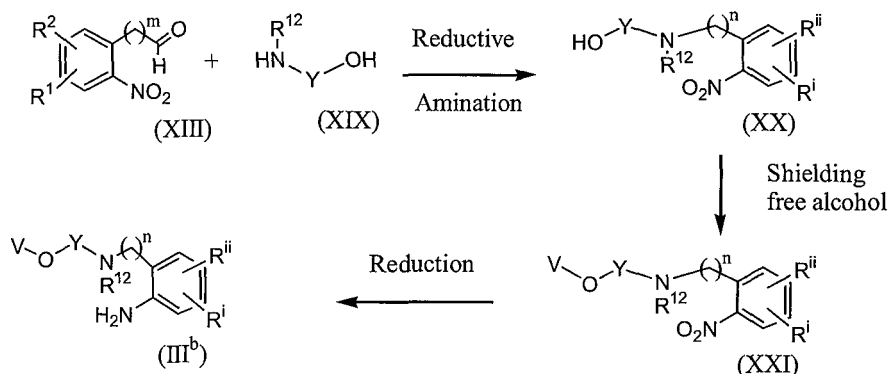


X represents a halogen such as for example, Cl, Br, and I
 V represents a protective group such as for example methylcarbonyl
 Rⁱ represents either R¹ or R⁵ as defined for the compounds of formula(I)
 hereinbefore and Rⁱⁱ represents either R² or R⁴ as defined for the
 compounds of formula(I) hereinbefore.

For those compounds of formula (I) where X^1 or X^2 represents NR^{16} -C₁₋₂alkyl- or -NR¹⁸-C₁₋₂alkyl- respectively, the suitable substituted anilines of formula (III^b) are generally prepared from the commercially available 2-nitro-benzaldehydes (XIII) and the amine substituted alcohols (XIX) by reductive amination under standard conditions, for example using NaBH₄ and titanium(IV)isopropoxide as reducing agents in ethanol as solvent, yielding in a first step the nitro-benzylamines of formula (XX).

Next the primary free alcohol is protected using art known procedures, for example, using an esterification reaction with acetic anhydride in the presence of pyridine. The thus obtained intermediate of formula (XXI) is subsequently reduced according to standard conditions, for example, using iron/acetic acid to yield the substituted anilines of formula (III^b) (Scheme 9).

Scheme 9



V represents a protective group such as for example methylcarbonyl

m = 0 or 1 and n = 1 or 2

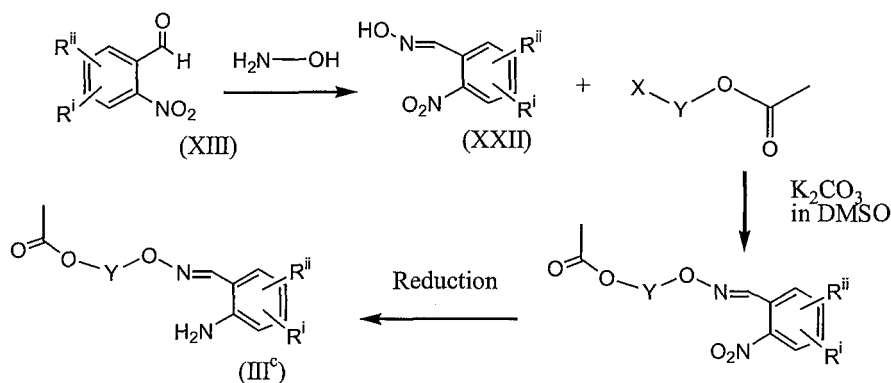
Rⁱ represents either R¹ or R⁵ as defined for the compounds of formula(I) hereinbefore and Rⁱⁱ represents either R² or R⁴ as defined for the compounds of formula(I) hereinbefore.

For those compounds of formula (I) where X¹ or X² represents -O-N=CH-, the suitable substituted anilines of formula (III^c) are generally prepared according to reaction scheme 10.

In a first step the known 2-nitro-benzaldehydes (XIII) are converted into the corresponding oxime (XXII) using, for example, the art known condensation reaction with hydroxylamine.

Next said oxime of formula XXII is allowed to react with an halogenated alkylacetate under alkaline conditions, for example using K₂CO₃ in DMSO, followed by reducing the nitro group, for example, with iron/acetic acid, to provide the suitable substituted aniline of formula (III^c).

Scheme 10



X represents a halogen such as for example Cl, Br, or I

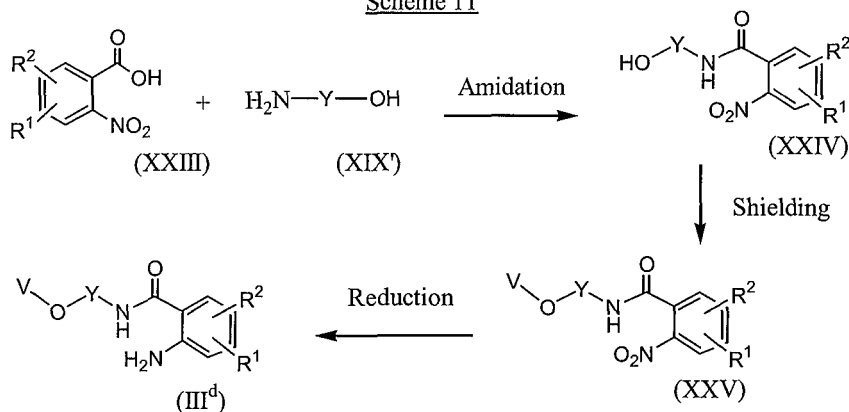
Rⁱ represents either R¹ or R⁵ as defined for the compounds of formula(I) hereinbefore and Rⁱⁱ represents either R² or R⁴ as defined for the compounds of formula(I) hereinbefore.

For those compounds where X¹ represents -O-, X² represents a direct bond and Y represents C₁₋₆alkyl-NH-CO-, the suitable substituted anilines of formula (III^d) are generally prepared according to reaction scheme 11.

In a first step the known 2-nitro-benzoic acids (XXIII) are amidated to the intermediates of formula (XXIV) under art known conditions, for example, using a hydroxylated amine of formula (XIX') that is added dropwise to a mixture of (XXIII) in CH₂Cl₂ in the presence of 1,1'-carbonylbis-1H-imidazole.

- 10 Next the primary free alcohol is protected using art known procedures, for example, using an esterification reaction with acetic anhydride in the presence of pyridine. The thus obtained intermediate of formula (XXV) is subsequently reduced according to standard conditions, for example, using iron/acetic acid to yield the substituted anilines of formula (III^d).

Scheme 11

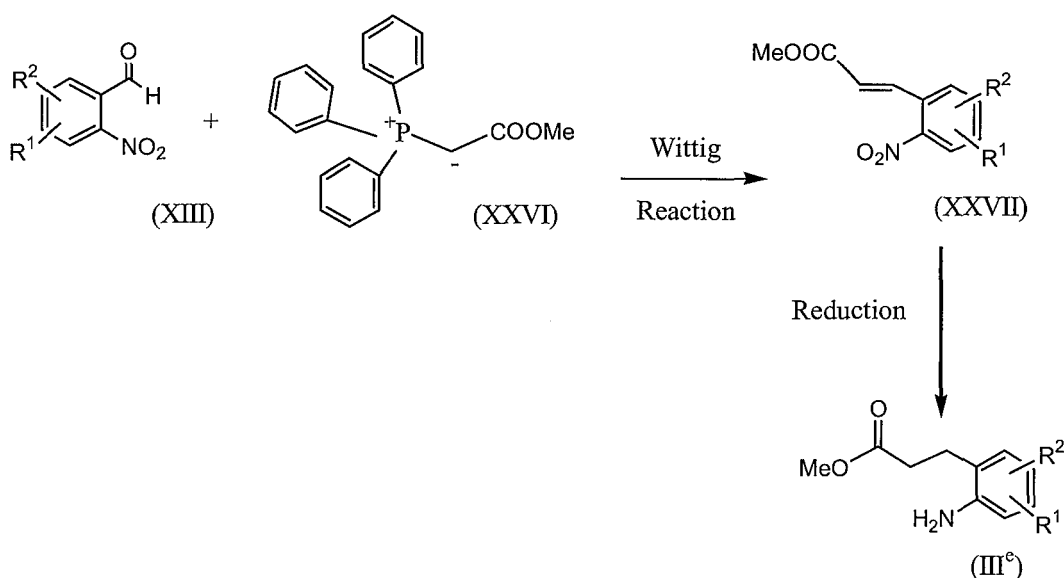


V represents a protective group such as for example methylcarbonyl

For those compounds where X² represents a direct bond the suitable substituted anilines of formula (III^e) are generally prepared according to reaction scheme 12.

- 5 In a first step the known 2-nitro-benzaldehydes (XIII) are alkenated to the intermediates of formula (XXVII) under art known conditions, for example, using the Wittig Reaction with the appropriate phosphonium salt of formula (XXVI). Following esterification of the free carboxylic acid under standard conditions for example, using ethanol under acidic conditions, the intermediate of formula (XXVIII) are reduced to yield the desired substituted anilines of formula (III^e).
- 10

Scheme 12



More specific examples for the synthesis of compounds of formula (I) are provided in the examples hereinafter.

Where necessary or desired, any one or more of the following further steps in any order may be performed :

- (i) removing any remaining protecting group(s);
- (ii) converting a compound of formula (I) or a protected form thereof into a further compound of formula (I) or a protected form thereof;
- (iii) converting a compound of formula (I) or a protected form thereof into a *N*-oxide, a salt, a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof;
- (iv) converting a *N*-oxide, a salt, a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof into a compound of formula (I) or a protected form thereof;
- (v) converting a *N*-oxide, a salt, a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof into another *N*-oxide, a pharmaceutically acceptable addition salt a quaternary amine or a solvate of a compound of formula (I) or a protected form thereof;
- (vi) where the compound of formula (I) is obtained as a mixture of (R) and (S) enantiomers resolving the mixture to obtain the desired enantiomer.

Compounds of formula (I), *N*-oxides, addition salts, quaternary amines and stereochemical isomeric forms thereof can be converted into further compounds according to the invention using procedures known in the art.

It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds may need to be blocked by protecting groups.

Functional groups, which are desirable to protect, include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), benzyl and tetrahydropyranyl. Suitable protecting groups for amino include *tert*-butyloxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C₍₁₋₆₎alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after a reaction step. The use of protecting groups is fully described in 'Protective Groups in Organic Synthesis' 2nd edition, T W Greene & P G M Wutz, Wiley Interscience (1991).

- 5 Additionally, the N-atoms in compounds of formula (I) can be methylated by art-known methods using CH₃-I in a suitable solvent such as, for example 2-propanone, tetrahydrofuran or dimethylformamide.

10 The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation of which some examples are mentioned hereinafter.

15 The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise
20 peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroalkanoic acids, e.g. peroacetic acid, alkylhydroperoxides, e.g. *t*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g.
25 dichloromethane, and mixtures of such solvents.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of
30 art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts
35 or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated

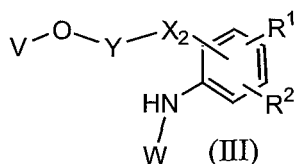
diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

5

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

- 10 Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures. However, in the synthesis of the compounds of formula (I), the present invention further provides;

- 15 a) the intermediates of formula (III)



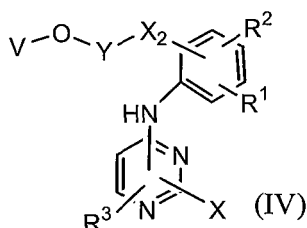
the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

- 20 V represents hydrogen or a protective group preferably selected from the group consisting of methylcarbonyl, t-butyl, methyl, ethyl, benzyl or trialkylsilyl;
W represents hydrogen or a protective group preferably selected from the group consisting of t-butyloxycarbonyl or benzyloxycarbonyl;
Y represents -O-C₁₋₅alkyl- with the oxygen atom attached to the phenyl ring,
25 -C₁₋₅alkyl-CO-NH-, C₁₋₃alkyl-CO-NH-, -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-,
-CO-NH-CR¹⁴R¹⁵-CO-, or -Het⁶-CO-, Het⁸-NH-C₁₋₃alkyl-CO-NH-;
X₂ represents a direct bond, -O-C₁₋₂alkyl- with the oxygen atom attached to the phenyl ring, CO, -CO-C₁₋₂alkyl-, NR¹⁸, -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-,
-Het²⁴-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
30 R¹ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-,
halo-phenyl-carbonylamino-, Het²⁰,
C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-, or R¹ represents
C₁₋₆alkyl substituted with one or where possible two or more substituents selected
from hydroxy, Het¹⁸ or halo;

- R² represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-,
C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or
di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-,
aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide,
5 C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- R¹³ each represents hydrogen, or C₁₋₄alkyl optionally substituted with hydroxy, amino,
mono- or di(C₁₋₄alkyl)amine, phenyl or C₁₋₄alkyloxy;
- R¹⁴ and R¹⁵ each independently represents hydrogen or C₁₋₄alkyl optionally substituted
with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl,
10 aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amino-,
imidazolyl or guanidino;
- R¹⁸ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl,
C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- Het⁶ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl
15 or piperidinyl wherein said Het⁶ is optionally substituted with one or where
possible two or more substituents selected from hydroxy, C₁₋₄alkyl,
hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het⁸ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl
or piperidinyl wherein said Het⁸ is optionally substituted with one or where
20 possible two or more substituents selected from hydroxy, C₁₋₄alkyl,
hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein siad
Het¹⁶ is optionally substituted with one or where possible two or more substituents
selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl
25 or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or
piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible
two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 30 Het²⁰ represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl,
furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl,
oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het²⁰ is optionally substituted
with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-,
C₁₋₄alkyl-oxy-C₁₋₄alkyl-, mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- 35 Het²² represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or
piperidinyl wherein said Het²² is optionally substituted with one or where possible

two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
Het²⁴ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl,
isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²⁴
5 is optionally substituted with one or where possible two or more substituents
selected from hydroxy, Het²⁵, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or
polyhydroxy-C₁₋₄alkyl-; and
Het²⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or
piperidinyl wherein said Het²⁵ is optionally substituted with one or where possible
10 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-.

b) the intermediates of formula (IV)



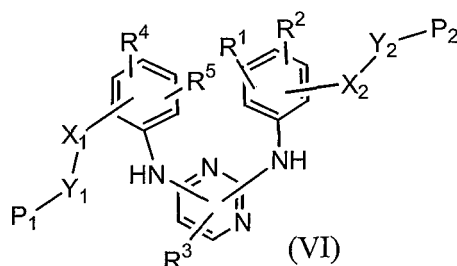
15 the pharmaceutically acceptable addition salts and the stereochemically isomeric forms
thereof, wherein
V represents hydrogen or a protective group preferably selected from the group
consisting of methylcarbonyl, t-butyl, methyl, ethyl, benzyl or trialkylsilyl;
20 Y represents -O-C₁₋₅alkyl- with the oxygen atom attached to the phenyl ring,
-C₁₋₅alkyl-CO-NH-, C₁₋₃alkyl-CO-NH-, -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-,
-CO-NH-CR¹⁴R¹⁵-CO-, or Het⁸-NH-C₁₋₃alkyl-CO-NH-;
X represents halo, in particular chloro or X represents C₁₋₄alkyl-sulfide or
C₁₋₄alkylsulfoxide;
25 X₂ represents a direct bond, -O-C₁₋₂alkyl- with the oxygen atom attached to the phenyl
ring, CO, -CO-C₁₋₂alkyl-, NR¹⁸, -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-,
-Het²⁴-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
R¹ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-,
halo-phenyl-carbonylamino-, Het²⁰,
30 C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-, or R¹ represents
C₁₋₆alkyl substituted with one or where possible two or more substituents selected
from hydroxy, Het¹⁸ or halo;

- R² represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono- or di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- R³ represents hydrogen, cyano, nitro, C₁₋₄alkyl- or C₁₋₄alkyl substituted with one or more substituents selected from halo, C₁₋₄alkyloxy or phenyl;
- R¹³ each represents hydrogen, or C₁₋₄alkyl optionally substituted with hydroxy, amino, mono- or di(C₁₋₄alkyl)amine, phenyl or C₁₋₄alkyloxy;
- 10 R¹⁴ and R¹⁵ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amino-, imidazolyl or guanidino;
- R¹⁸ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- 15 Het⁶ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁶ is optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- 20 Het⁸ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁸ is optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁶ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 25 Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 30 Het²⁰ represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het²⁰ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl-, mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- 35

- Het²² represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 5 Het²⁴ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²⁴ is optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²⁵, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-; and
- 10 Het²⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-.
- 15 In particular the intermediates of formula (III) or (IV) wherein one or more of the following restrictions apply;
- i) V represents hydrogen, methyl, t-butyl or ethyl;
 - ii) Y represents -O-C₁₋₅alkyl-, -C₁₋₅alkyl-CO-NH-, C₁₋₃alkyl-CO-NH-, -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-, -CO-NH-CR¹⁴R¹⁵-CO-, or Het⁸-NH-C₁₋₃alkyl-CO-NH-;
 - 20 iii) X² represents a direct bond, -O-C₁₋₂alkyl-, NR¹⁸, -NR¹⁸-C₁₋₂alkyl-, -CH₂-, -CO-NR¹⁹-, Het²⁴ or -Het²⁴-C₁₋₂alkyl-;
 - iv) X² represents CO-NR¹⁹- or -Het²⁴-C₁₋₂alkyl-;
 - v) R¹ represents hydrogen, halo, C₁₋₆alkoxy-, Het²⁰ or R¹ represents C₁₋₆alkoxy-substituted with halo, Het¹ or C₁₋₄alkyloxy-;
 - 25 vi) R² represents hydrogen, cyano, halo or hydroxy, preferably halo, more in particular fluoro or chloro;
 - vii) R¹³ represents hydrogen or C₁₋₄alkyl;
 - viii) R¹⁴ and R¹⁵ each independently represent hydrogen or C₁₋₄alkyl optionally substituted with mono- or di(C₁₋₄alkyl)-amino-;
 - 30 ix) R¹⁸ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl; in particular hydrogen;
 - x) Het⁶ represents a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl wherein said heterocycle is optionally substituted with hydroxy;
 - xi) Het⁸ represents a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl wherein said heterocycle is optionally substituted with hydroxy;
 - 35 xii) Het²⁰ represents morpholinyl;

- xiii) Het²² represents pyrrolidinyl, quinolinyl, isoquinolinyl, morpholinyl, piperazinyl or piperidinyl;
 xiv) Het²⁴ represents pyrrolidinyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²⁴ is optionally substituted with hydroxy or Het²²-carbonyl.

c) the intermediates of formula (VI)



the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

P₁ and P₂ each independently represent hydroxy, halo, hydroxycarbonyl-, halocarbonyl-, amino or-NHR²⁹;

Y₁ and Y₂ each independently represent C₁₋₇alkyl, C₃₋₇alkenyl or C₃₋₇alkynyl wherein said C₁₋₇alkyl, C₃₋₇alkenyl, C₃₋₇alkynyl are optionally substituted with one or where possible two or more substituents selected from amino, mono- or di(C₁₋₄alkyl)amino, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfonyl and C₁₋₄alkyloxycarbonylamino;

or Y₁ and Y₂ each independently represent Het²⁷, Het²⁸-CO, Het²⁹-C₁₋₅alkyl, CR⁸R⁹-NH, CR²³R²⁴-NH-CO, CR²⁰R²¹-CO, CR²⁵R²⁶-CO-NH, CO-C₁₋₃alkyl, NH-CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂, CH₂-CO-NH-C₁₋₃alkyl or C₁₋₃alkyl-NH;

X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹⁶, -NR¹⁶-C₁₋₂alkyl-, -CH₂-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;

X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹⁸, -NR¹⁸-C₁₋₂alkyl-, -CH₂-, -CO-NR¹⁹-, -Het²⁴-, -Het²⁴-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;

R¹ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-, halo-phenyl-carbonylamino-, Het²⁰,

- C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-, or R¹ represents C₁₋₆alkyl substituted with one or where possible two or more substituents selected from hydroxy, Het¹⁸ or halo;
- R² represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-,
 5 C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- R³ represents hydrogen, cyano, nitro, C₁₋₄alkyl, or C₁₋₄alkyl substituted with one or
 10 more substituents selected from halo, C₁₋₄alkyloxy-, amino-, mono-or di(C₁₋₄alkyl)amino-, C₁₋₄alkyl-sulfonyl- or phenyl;
- R⁴ represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-,
 15 aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- R⁵ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-, halo-phenyl-carbonylamino-, Het²¹,
 C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-, or R⁵ represents
 20 C₁₋₆alkyl substituted with one or where possible two or more substituents selected from hydroxy, Het¹⁹ or halo;
- R⁸, R⁹, R²³ and R²⁴ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with cyano, phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl, C₃₋₆cycloalkyl,
 25 C₁₋₄alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amine-, imidazolyl or guanidino;
- R¹¹ represents hydrogen, C₁₋₄alkyl or represent mono-or di(C₁₋₄alkyl)amino-C₁₋₄alkyl-carbonyl- optionally substituted with hydroxy, pyrimidinyl, mono- or di(C₁₋₄alkyl)amine or C₁₋₄alkyloxy;
- 30 R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- R¹⁷ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, Het¹⁴, Het¹⁵-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- R²⁰, R²¹, R²⁵ and R²⁶ each independently represents hydrogen or C₁₋₄alkyl optionally
 35 substituted with cyano, phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl, C₃₋₆cycloalkyl,

- aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amino-,
imidazolyl or guanidino;
- R²⁹ represents phenyl, Het³⁰ or C₁₋₄alkyl wherein said R²⁹ is optionally substituted with
one or where possible two or more substituents selected from hydroxy, amino,
5 mono- or di(C₁₋₄alkyl)amino, phenyl, Het³¹ or C₁₋₄alkyloxy-;
- Het¹ represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl,
furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl,
oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹ is optionally substituted
with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-,
10 C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- Het² represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl,
furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl,
oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het² is optionally substituted
with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-,
15 C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said
pyrrolidinyl or piperazinyl are optionally substituted with one or where possible
two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 20 Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or
piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible
two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said
25 pyrrolidinyl or piperidinyl are optionally substituted with one or where possible
two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or
piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible
30 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁸ and Het¹⁹ each independently represents a heterocycle selected from piperidinyl,
morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl,
imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹⁸ or
35 Het¹⁹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl,
phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-
carbonyl-;

- Het²⁰ and Het²¹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het²⁰ or Het²¹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- Het²² represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²⁵, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het²⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het²⁷ and Het²⁹ each independently represent a heterocycle selected from pyrrolidinyl, -pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²⁷ and Het²⁹ are optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²²-carbonyl-, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het²⁸ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het²⁸ is optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het³⁰ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said heterocycle is optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl, C₁₋₄alkyloxy-C₁₋₄alkyl or polyhydroxyC₁₋₄alkyl-; and
- Het³¹ represents a heterocycle selected from morpholinyl, pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het³¹ is optionally substituted with one or where possible two or more substituents selected from

hydroxy, C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl, C₁₋₄alkyloxy-C₁₋₄alkyl or polyhydroxyC₁₋₄alkyl-.

In another embodiment the present invention provides the intermediates of formula
5 (VI) wherein one or more of the following restrictions apply;

P₁ and P₂ each independently represent hydroxy, halo, hydroxycarbonyl-, halocarbonyl-, amino or NHR²⁹;

Y₁ and Y₂ each independently represent C₁₋₇alkyl, C₃₋₇alkenyl, Het²⁷, Het²⁸-CO, CR⁸R⁹-NH, CR²³R²⁴NH-CO, CO-C₁₋₃alkyl, NH-CO-C₁₋₃alkyl,

10 C₁₋₃alkyl-NR¹¹-CH₂, CH₂-CO-NH-C₁₋₃alkyl or C₁₋₃alkyl-NH; in particular Y₁ and Y₂ each independently represent C₁₋₇alkyl, C₃₋₇alkenyl, Het²⁷, Het²⁸-CO, CR⁸R⁹-NH,

CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂ or CH₂-CO-NH-C₁₋₃alkyl; in a more particular embodiment Y₁ and Y₂ each independently represent Het²⁷, Het²⁸-CO, CR⁸R⁹-NH,

15 CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂ or CH₂-CO-NH-C₁₋₃alkyl;

X¹ represents a direct bond, O, O-C₁₋₂alkyl, CO-C₁₋₂alkyl, NR¹⁶-C₁₋₂alkyl or CO-NR¹⁷;

X² represents a direct bond, O, O-C₁₋₂alkyl, CO-C₁₋₂alkyl, NR¹⁸-C₁₋₂alkyl, CO-NR¹⁹, or Het²⁴-C₁₋₂alkyl;

R¹ represents hydrogen, halo, C₁₋₆alkyloxy-, or C₁₋₆alkyloxy substituted with Het¹ or
20 C₁₋₄alkyloxy;

R² represents hydrogen or halo;

R³ represents hydrogen, cyano or nitro; in particular hydrogen or cyano;

R⁴ represents hydrogen or halo;

R⁵ represents hydrogen, halo, C₁₋₆alkyloxy-, or C₁₋₆alkyloxy substituted with Het² or
25 C₁₋₄alkyloxy;

R⁸, R⁹, R²³ and R²⁴ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or di(C₁₋₄alkyl)-amine or imidazolyl; in particular R⁸, R⁹, R²³ and R²⁴ each independently represents hydrogen or C₁₋₄alkyl;

30 R¹¹ represents hydrogen or C₁₋₄alkyl;

R¹⁶, R¹⁷, R¹⁸ and R¹⁹ represent hydrogen;

R²⁹ represents hydrogen, C₁₋₄alkyl, or Het³¹-C₁₋₄alkyl; in particular R²⁹ represents hydrogen or Het³¹-C₁₋₄alkyl;

Het¹ represents morpholinyl;

35 Het² represents morpholinyl;

Het²⁷ represents pyrrolidinyl or piperazinyl;

Het²⁸ represents pyrrolidinyl or piperazinyl; or

Het³¹ represents morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het³¹ is optionally substituted with hydroxy.

It is also an object of the present invention to provide the intermediates of formula (VII) wherein;

P₁ and P₂ each independently represent hydroxy, halo, hydroxycarbonyl-, halocarbonyl-, amino or -NHR²⁹;

Y₁ and Y₂ each independently represent C₁₋₇alkyl, C₃₋₇alkenyl, Het²⁷, Het²⁸-CO, Het²⁹-C₁₋₅alkyl, L²-NH, L¹-NH-CO, L³-CO, L³-CO-NH, CO-C₁₋₆alkyl,

NH-CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂, or CH₂-CO-NH-C₁₋₃alkyl; in particular Y₁ and Y₂ each independently represent C₁₋₇alkyl, C₃₋₇alkenyl, Het²⁷, Het²⁸-CO, L¹-NH, CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂ or CH₂-CO-NH-C₁₋₃alkyl; in a more particular embodiment Y₁ and Y₂ each independently represent Het²⁷, Het²⁸-CO, L¹-NH, CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂ or CH₂-CO-NH-C₁₋₃alkyl;

X¹ represents a direct bond, O, -O-C₁₋₂alkyl, CO, CO-C₁₋₂alkyl, NR¹⁶-C₁₋₂alkyl, CO-NR¹⁷, Het²³-C₁₋₂alkyl, or C₁₋₂alkyl;

X² represents a direct bond, O, -O-C₁₋₂alkyl, CO, CO-C₁₋₂alkyl, NR¹⁸-C₁₋₂alkyl, CO-NR¹⁶, Het²⁴-C₁₋₂alkyl, or C₁₋₂alkyl;

R¹ represents hydrogen, halo, C₁₋₆alkyloxy or C₁₋₆alkyloxy substituted with Het¹ or C₁₋₄alkyloxy;

R² represents hydrogen or halo;

R³ represents hydrogen or cyano;

R⁴ represents hydrogen or halo;

R⁵ represents hydrogen, halo, C₁₋₆alkyloxy or C₁₋₆alkyloxy substituted with Het² or C₁₋₄alkyloxy;

R¹¹ represents hydrogen or C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl;

R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl;

R¹⁷ and R¹⁹ each independently represent hydrogen;

L¹ represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, mono- or di(C₁₋₄alkyl)amino, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl, imidazolyl or C₃₋₆cycloalkyl; in particular L¹ represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or di(C₁₋₄alkyl)-amine or imidazolyl

L² represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, mono- or di(C₁₋₄alkyl)amino, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl, imidazolyl or C₃₋₆cycloalkyl;

L³ represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, mono- or di(C₁₋₄alkyl)amino, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl, imidazolyl or C₃₋₆cycloalkyl;

Het¹ represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het¹ represents morpholinyl or piperazinyl; more in particular Het¹ represents morpholinyl;

Het² represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het² represents morpholinyl or piperazinyl; more in particular Het² represents morpholinyl;

Het²² represents a heterocycle selected from morpholinyl, piperazinyl or piperidinyl wherein said Het²² is optionally substituted with C₁₋₄alkyl;

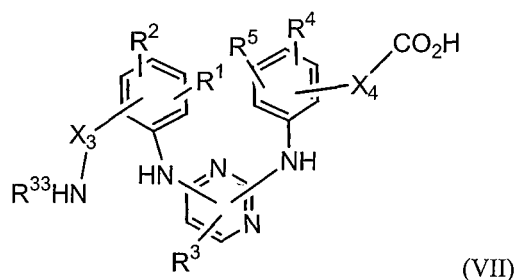
Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl, wherein said Het²³ and Het²⁴ is optionally substituted with Het²²-carbonyl;

Het²⁷ and Het²⁹ each independently represent a heterocycle selected from morpholinyl, pyrrolidinyl, --pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²⁷ and Het²⁹ are optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²²-carbonyl-, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-; in particular Het²⁷ and Het²⁹ are each independently selected from morpholinyl, piperazinyl or pyrrolidinyl; more in particular Het²⁷ and Het²⁹ are each independently selected from piperazinyl or pyrrolidinyl;

Het²⁸ represents a heterocycle selected from morpholinyl, pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het²⁸ is optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-; in particular Het²⁸ is selected from morpholinyl, piperazinyl or pyrrolidinyl; more in particular Het²⁷ and Het²⁹ is selected from piperazinyl or pyrrolidinyl.

30

d) the intermediate of formula (VII)



the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

- X_3 and X_4 each independently represent a direct bond, C_{1-7} alkyl, C_{3-7} alkenyl, C_{3-7} alkynyl, wherein said C_{1-7} alkyl, C_{3-7} alkenyl, C_{3-7} alkynyl are optionally substituted with one or where possible two or more substituents selected from amino, mono- or di(C_{1-4} alkyl)amino, aminosulfonyl, mono- or di(C_{1-4} alkyl)aminosulfonyl, C_{1-4} alkylsulfide, C_{1-4} alkylsulfoxide, C_{1-4} alkylsulfonyl and C_{1-4} alkyloxycarbonylamino;
- or X_3 and X_4 each independently represent C_{1-5} alkyl-O- C_{1-5} alkyl, C_{1-5} alkyl-NR³⁰- C_{1-5} alkyl, C_{1-2} alkyl-CO-Het¹⁰, Het²³, O- C_{1-2} alkyl with the oxygen atom attached to the phenyl ring or CR⁸R⁹;
- R¹ represents hydrogen, cyano, halo, hydroxy, formyl, C_{1-6} alkoxy-, C_{1-6} alkyl-, halo-phenyl-carbonylamino-, Het²⁰,
- C_{1-6} alkoxy- substituted with halo, Het¹ or C_{1-4} alkyloxy-, or R¹ represents C_{1-6} alkyl substituted with one or where possible two or more substituents selected from hydroxy, Het¹⁸ or halo;
- R² represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C_{1-4} alkyloxycarbonyl-, C_{1-4} alkylcarbonyl-, aminocarbonyl-, mono-or di(C_{1-4} alkyl)aminocarbonyl-, C_{1-4} alkyl-, C_{2-6} alkynyl-, C_{3-6} cycloalkyloxy-, aminosulfonyl, mono-or di(C_{1-4} alkyl)aminosulfonyl, C_{1-4} alkylsulfide, C_{1-4} alkylsulfoxide, C_{1-4} alkylsulfide or C_{1-6} alkoxy-;
- R³ represents hydrogen, cyano, nitro, C_{1-4} alkyl, or C_{1-4} alkyl substituted with one or more substituents selected from halo, C_{1-4} alkyloxy-, amino-, mono-or di(C_{1-4} alkyl)amino-, C_{1-4} alkyl-sulfonyl- or phenyl;
- R⁴ represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C_{1-4} alkyloxycarbonyl-, C_{1-4} alkylcarbonyl-, aminocarbonyl-, mono-or di(C_{1-4} alkyl)aminocarbonyl-, C_{1-4} alkyl-, C_{2-6} alkynyl-, C_{3-6} cycloalkyloxy-, aminosulfonyl, mono-or di(C_{1-4} alkyl)aminosulfonyl, C_{1-4} alkylsulfide, C_{1-4} alkylsulfoxide, C_{1-4} alkylsulfide or C_{1-6} alkoxy-;
- R⁵ represents hydrogen, cyano, halo, hydroxy, formyl, C_{1-6} alkoxy-, C_{1-6} alkyl-, halo-phenyl-carbonylamino-, Het²¹,

C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-, or R⁵ represents C₁₋₆alkyl substituted with one or where possible two or more substituents selected from hydroxy, Het¹⁹ or halo;

R⁸ and R⁹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, C₁₋₄alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amine-, imidazolyl, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl, C₃₋₆cycloalkyl or guanidino; in particular R⁸ and R⁹ each independently represent hydrogen or C₁₋₄alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, C₁₋₄alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amine-, imidazolyl, or guanidino; even more particular R⁸ and R⁹ each independently represent hydrogen or C₁₋₄alkyl optionally substituted with phenyl, methylsulfide or mono-or di(C₁₋₄alkyl)amine;

R³⁰ represents hydrogen, C₁₋₄alkyl, Het¹¹, Het¹²-C₁₋₄alkyl, phenyl-C₁₋₄alkyl, phenyl or mono- or di(C₁₋₄alkyl)amino-C₁₋₄alkyl-carbonyl wherein said R³⁰ is optionally substituted with hydroxy, amino, mono- or di(C₁₋₄alkyl)amino, pyrimidinyl or C₁₋₄alkyloxy;

R³³ represents hydrogen, C₁₋₄alkyl, Het¹⁴ or C₁₋₄alkyl substituted with one or where possible two or more substituents selected from hydroxy, amino, mono- or di(C₁₋₄alkyl)amino, phenyl, Het¹⁵ or C₁₋₂alkyloxy;

Het¹ represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;

Het² represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het² is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;

Het¹⁰ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het¹⁰ is optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;

Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents

- selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible
5 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperazinyl are optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
10 hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 15 Het¹⁸ and Het¹⁹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹⁸ or Het¹⁹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-
20 carbonyl-;
- Het²⁰ and Het²¹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het²⁰ or Het²¹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl,
25 phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- Het²² represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl,
30 hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het²³ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²³ is optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²⁵, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or
35 polyhydroxy-C₁₋₄alkyl-; and
- Het²⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²⁵ is optionally substituted with one or where possible

two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-, provided that said intermediate of formula (VII) is other than 2-[[2-[(3-aminophenyl)amino]-4-pyrimidinyl]amino]-Benzoic acid [604801-24-3].

5

In another embodiment the present invention provides the intermediates of formula (VII) wherein one or more of the following restrictions apply;

X₃ and X₄ each independently represent a direct bond, C₁₋₇alkyl, C₃₋₇alkenyl, C₁₋₅alkyl-NR³⁰-C₁₋₅alkyl, Het²³, CR⁸R⁹, or O-C₁₋₂alkyl with the oxygen atom attached to the phenyl ring;

10

R¹ represents hydrogen, halo, C₁₋₆alkyloxy-, or C₁₋₆alkyloxy substituted with Het¹ or C₁₋₄alkyloxy;

R² represents hydrogen or halo;

R³ represents hydrogen, cyano or nitro; in particular hydrogen or cyano;

15 R⁴ represents hydrogen or halo;

R⁵ represents hydrogen, halo, C₁₋₆alkyloxy-, or C₁₋₆alkyloxy substituted with Het² or C₁₋₄alkyloxy;

R⁸ and R⁹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or di(C₁₋₄alkyl)-amine-, or imidazolyl;

20

R³⁰ represents hydrogen, C₁₋₄alkyl or Het¹²-C₁₋₄alkyl;

R³³ represents hydrogen, C₁₋₄alkyl or Het¹⁵-C₁₋₄alkyl;

Het¹ represents morpholinyl;

Het² represents morpholinyl;

25 Het¹² represents pyrrolidinyl or piperazinyl wherein said Het¹² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl,

C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-; in particular Het¹² represents pyrrolidinyl or piperazinyl;

Het¹⁵ represents pyrrolidinyl or piperazinyl wherein said Het¹⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl,

30

C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-; in particular Het¹⁵ represents pyrrolidinyl or piperazinyl;

or

Het²³ represents a heterocycle selected from pyrrolidinyl, decahydroquinolinyl or

35 pyridinyl wherein said Het²³ is optionally substituted with one or where possible two or more substituents selected from hydroxy or C₁₋₄alkyl.

In a further embodiment of the present invention, the intermediates of formula (VII) are characterized in that the the two aniline residues are bound to the pyrimidine ring at positions 2, 4 or 4,6 respectively; X₃ and X₄ substituent are at position 3'; R¹ and R⁴ are at position 4' and R² and R⁵ are at position 5'.

5

It is also an object of the present invention to provide the use of the intermediates of formula (III), (IV), (VI), (VII), (XXIX), (XXX), (XXXI), (XXXII), (XXXIII) in the synthesis of a macrocyclic kinase inhibitor such as for the compounds of formula (I).

10 As described in the experimental part hereinafter, the growth inhibitory effect and anti-tumour activity of the present compounds has been demonstrated in vitro, in enzymatic assays on the receptor tyrosine kinases EGFR, ErbB2, ErbB4, Flt3, BLK or the Sar kinase family such as for example Lyn, Yes cSRC. In an alternative assay, the growth inhibitory effect of the compounds was tested on a number of carcinoma cell lines, in
15 particular in the ovarian carcinoma cell line SKOV3 and the squamous carcinoma cell line A431 using art known cytotoxicity assays such as MTT.

Accordingly, the present invention provides the compounds of formula (I) and their pharmaceutically acceptable *N*-oxides, addition salts, quaternary amines and
20 stereochemically isomeric forms for use in therapy. More particular in the treatment or prevention of cell proliferation mediated diseases. The compounds of formula (I) and their pharmaceutically acceptable *N*-oxides, addition salts, quaternary amines and the stereochemically isomeric forms may hereinafter be referred to as compounds according to the invention.

25

Disorders for which the compounds according to the invention are particularly useful are atherosclerosis, restenosis, cancer and diabetic complications e.g. retinopathy.

In view of the utility of the compounds according to the invention, there is provided a
30 method of treating a cell proliferative disorder such as atherosclerosis, restenosis and cancer, the method comprising administering to an animal in need of such treatment, for example, a mammal including humans, suffering from a cell proliferative disorder, a therapeutically effective amount of a compound according to the present invention.

35 Said method comprising the systemic or topical administration of an effective amount of a compound according to the invention, to animals, including humans. One skilled in the art will recognize that a therapeutically effective amount of the kinase inhibitors

of the present invention is the amount sufficient to induce the growth inhibitory effect and that this amount varies *inter alia*, depending on the size, the type of the neoplasia, the concentration of the compound in the therapeutic formulation, and the condition of the patient. Generally, an amount of kinase inhibitor to be administered as a
5 therapeutic agent for treating cell proliferative disorder such as atherosclerosis, restenosis and cancer, will be determined on a case by case by an attending physician.

Generally, a suitable dose is one that results in a concentration of the kinase inhibitor at the treatment site in the range of 0.5 nM to 200 μ M, and more usually 5 nM to 10 μ M.
10 To obtain these treatment concentrations, a patient in need of treatment likely will be administered between 0.01 mg/kg to 500 mg/kg body weight, in particular from 10 mg/kg to 250 mg/kg body weight. As noted above, the above amounts may vary on a case-by-case basis. In these methods of treatment the compounds according to the invention are preferably formulated prior to admission. As described herein below,
15 suitable pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

In yet a further aspect, the present invention provides the use of the compounds
20 according to the invention in the manufacture of a medicament for treating any of the aforementioned cell proliferative disorders or indications.

The amount of a compound according to the present invention, also referred to here as the active ingredient, which is required to achieve a therapeutical effect will be, of
25 course, vary with the particular compound, the route of administration, the age and condition of the recipient, and the particular disorder or disease being treated. A suitable daily dose would be from 0.01 mg/kg to 500 mg/kg body weight, in particular from 10 mg/kg to 250 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between one and four intakes per
30 day.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. Accordingly, the present invention further provides a pharmaceutical composition comprising a compound according to the
35 present invention, together with a pharmaceutically acceptable carrier or diluent. The carrier or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The pharmaceutical compositions of this invention may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al. Remington's Pharmaceutical Sciences (18th ed., Mack Publishing
5 Company, 1990, see especially Part 8 : Pharmaceutical preparations and their Manufacture). A therapeutically effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical
10 compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as oral, percutaneous or parenteral administration; or topical administration such as via inhalation, a nose spray, eye drops or via a cream, gel, shampoo or the like. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water,
15 glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will
20 usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case
25 appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the
30 administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical
35 compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity

of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and
5 segregated multiples thereof.

Experimental part

The following examples illustrate the present invention.

Hereinafter, "BINAP" is defined as [1,1'-binaphthalene]-2,2'-diylbis[diphenyl-
5 phosphine, "DMF" is defined as *N,N*-dimethylformamide, "DCM" is defined as
dichloromethane, "DIAD" is defined as diazenedicarboxylic acid, bis(1-methylethyl)
ester, "DIPE" is defined as diisopropyl ether, "DIPEA" (=DIEA, CAS 7087-68-5) is
defined as *N*-ethyl-*N*-(1-methylethyl)-2-propanamine, "DMSO" is defined as
dimethylsulfoxide, "DMF" is defined as *N,N*-dimethylformamide, "EDC" is defined as
10 *N*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine, monohydrochloride,
"EtOAc" is defined as ethyl acetate, "EtOH" is defined as ethanol, "HBTU" is defined
as 1-[bis(dimethylamino)methylene]-1*H*-Benzotriazolium, hexafluorophosphate(1-),
3-oxide, "MeOH" is defined as methanol, "NMP" is defined as 1-methyl-2-
pyrrolidinone, "TFA" is defined as trifluoroacetic acid, "THF" is defined as
15 tetrahydrofuran, "TIS" is defined as triisopropylsilane

A. Preparation of the intermediates

Example A1

Preparation of intermediate 1 5-pyrimidinecarbonitrile, 2,4-bis[[3-(2- propenyloxy)phenyl]amino]-

A mixture of 3-(2-propenyloxy)-benzenamine (max. 0.02 mol), 2,4-dichloro-5-
pyrimidinecarbonitrile (0.009 mol) and DIPEA (0.03 mol) in acetonitrile (200 ml) was
20 stirred and refluxed for 16 hours. The solvent was evaporated under reduced pressure.
The residue was taken up into diglyme and stirred for 4 hours at 100°C, then stirred
overnight at 100°C. The solvent was evaporated under reduced pressure. The residue
was purified twice by column chromatography over silica gel (eluent: DCM/MeOH
from 99/1 to 97/3). The product fractions were collected and the solvent was
25 evaporated under reduced pressure, yielding 1.2 g (33.4%) of intermediate 1.

Example A2

a) Preparation of intermediate 2 benzoic acid, 3-[[5-cyano-2-(methylthio)-4- pyrimidinyl]amino]-, 1,1-dimethylethyl ester

A mixture of 4-chloro-2-(methylthio)-5-pyrimidinecarbonitrile (0.010 mol), 3-amino-
benzoic acid, 1,1-dimethylethyl ester (0.010 mol) and DIPEA (0.010 mol) in 2-
30 propanol p.a. (50 ml) was stirred and refluxed for 1 hour, then a small amount of ice
was added and the obtained cloudy mixture was allowed to cool. The precipitate was

filtered off and dried, yielding 2.816 g (82 %) of intermediate 2, melting point 162-164°C.

b) Preparation of intermediate 3 benzoic acid, 3-[[5-cyano-2-(methylsulfonyl)-4-pyrimidinyl]amino]-, 1,1-dimethylethyl ester

A mixture of intermediate 2 (0.0082 mol) in DCM p.a. (80 ml) and MeOH p.a. (10 ml) was stirred at room temperature, then 3-chlorobenzenecarboxylic acid (0.020 mol) was added in small portions over 30 minutes and the reaction mixture was stirred for 4 hours at room temperature. The mixture was washed with a NaHCO₃ soln. (0.020 mol) and the layers were separated. The organic layer was washed again with water, dried, filtered off and the solvent was evaporated. The residue was purified by Flash column chromatography (eluent: DCM/MeOH 100/0 to 98/2). The product fractions were collected and the solvent was evaporated. The residue was crystallised from DIPE/acetonitrile (10/1), then the precipitate was filtered off and dried, yielding 1.742 g (56 %) of intermediate 3.

c) Preparation of intermediate 4 benzoic acid, 3-[[5-cyano-2-[[3-[2-[(1,1-dimethylethoxy)carbonyl]amino]ethoxy]phenyl]amino]-4-pyrimidinyl]amino]-, 1,1-dimethylethyl ester

A mixture of intermediate 3 (0.001 mol) and [2-(3-aminophenoxy)ethyl]- carbamic acid, 1,1-dimethylethyl ester (0.001 mol) in DMSO p.a. dried on molecular sieves (5 ml) was stirred for 2 hours at 120°C and then the reaction mixture was allowed to cool. The mixture was poured out into water and stirred overnight. The resulting precipitate was filtered off and dried, yielding 0.700 g of intermediate 4, which was combined with another fraction which was made on the same way and further purified by column chromatography (eluent: DCM/MeOH 98/2). The desired product fractions were collected and the solvent was evaporated, yielding 0.700 g of intermediate 4.

d) Preparation of intermediate 5 benzoic acid, 3-[[2-[[3-(2-aminoethoxy)phenyl]amino]-5-cyano-4-pyrimidinyl]amino]- trifluoroacetic acid salt

A mixture of intermediate 4 (0.00128 mol) in DCM (15 ml) was stirred at room temperature and then a mixture of TFA (0.5 ml) in DCM (5 ml) was added dropwise. The resulting mixture was stirred for 20 hours at room temperature and extra TFA (0.5 ml) in DCM (4.5 ml) was added. The reaction mixture was stirred and refluxed for 20 hours and then again extra TFA (2 ml) was added. The mixture was stirred and refluxed for 6 hours more and was then left to stand over the weekend. The solvent was evaporated and the obtained residue was stirred in DIPE/acetonitrile. The resulting precipitate was filtered off and dried, yielding 0.534 g (82 %) of intermediate 5, isolated as a trifluoroacetic acid salt.

Example A3a) Preparation of intermediate 6 carbamic acid, [4-(3-nitrophenoxy)butyl]-, 1,1-dimethylethyl ester

A mixture of (4-hydroxybutyl)-carbamic acid, 1,1-dimethylethyl ester (0.063 mol), 3-nitro-phenol (0.05 mol) and triphenyl-phosphine (0.05 mol) in THF (250 ml) was stirred at 0°C, then bis (1-methylethyl)diazenedicarboxylate (0.05 mol) was added dropwise at 0°C and the reaction mixture was allowed to reach room temperature. After stirring for 1 hour at ambient temperature, the solvent was evaporated and the obtained residue was purified by short column chromatography (eluent: DCM). The product fractions were collected and the solvent was evaporated. This residue (13 g) was then crystallised from petroleum-benzin/DIPE and the desired product was collected, yielding 16 g of intermediate 6, melting point 90°C.

b) Preparation of intermediate 7 carbamic acid, [4-(3-aminophenoxy)butyl]-, 1,1-dimethylethyl ester

A mixture of intermediate 6 (0.06 mol) in MeOH (250 ml) was hydrogenated at 50°C with Pd/C (2 g) as a catalyst in the presence of thiophene solution (1 ml). After uptake of H₂ (3 equiv.), the catalyst was filtered over dicalite and the filtrate was evaporated, yielding 14 g (100 %) of intermediate 7.

c) Preparation of intermediate 8 carbamic acid, [4-[3-[(2-chloro-4-pyrimidinyl)amino]phenoxy]butyl]-, 1,1-dimethylethyl ester

A mixture of 2,4-dichloro-pyrimidine (0.01 mol), intermediate 7 (0.011 mol) and DIPEA (0.015 mol) in EtOH (150 ml) was stirred and refluxed for 20 hours and then the solvent was evaporated. The obtained residue was dissolved in water and the solution was extracted with DCM. The organic layer was separated, dried (MgSO₄) and the solvent was evaporated. The residue was crystallised from DIPE and the resulting precipitate was collected, yielding 2.1 g (55.3 %) of intermediate 8.

d) Preparation of intermediate 9 acetic acid, [3-[[4-[[3-(4-aminobutoxy)phenyl]amino]-2-pyrimidinyl]amino]phenoxy]-

A mixture of intermediate 8 (0.0023 mol), (3-aminophenoxy)- acetic acid, 1,1-dimethylethyl ester (0.0030 mol) and HCl/2-propanol (2 drops) in 2-propanol/water (4/1) (100 ml) was stirred and refluxed over the weekend and then HCl/2-propanol (10 ml) was added. The reaction mixture was stirred and refluxed for 2 hours, then cooled and neutralised to pH 7 with a 36 % HCl solution. The resulting precipitate was filtered off, washed with water and dried (vac.) The obtained solids (1.2 g) were dissolved in sodium hydroxide 10% solution (100 ml) and then the resulting mixture was stirred and

refluxed for 20 hours. After neutralising the mixture with a 36 % HCl solution, the precipitate was filtered off, washed with water and dried (vac.), yielding 1.2 g (100 %) of intermediate 9.

5 Example A4

a) Preparation of intermediate 10 carbamic acid, [2-[[[(3-nitrophenyl)methyl]amino]-2-oxoethyl]-, 1,1-dimethylethyl ester

EDC (0.031 mol) was added to a mixture of 3-nitro- benzenemethanamine, monohydrochloride (0.026 mol), *N*-[(1,1-dimethylethoxy)carbonyl]- glycine (0.031 mol) and triethylamine (0.065 mol) in DMF (q.s.) at room temperature and then the reaction mixture was reacted for 3 hours at room temperature. After an aqueous work-
10 up with a 10 % citric acid solution, with water, with an aqueous NaHCO₃ solution and with NaCl, the organic layer was dried and the solvent was evaporated, yielding 3.66 g (46 %) of intermediate 10.

b) Preparation of intermediate 11 carbamic acid, [2-[[[(3-aminophenyl)methyl]amino]-2-oxoethyl]-, 1,1-dimethylethyl ester

A mixture of intermediate 10 (0.012 mol) in MeOH (30 ml) and THF (20 ml) was hydrogenated with Pd/C 10% (1 g) as a catalyst in the presence of thiophene solution (1
15 ml). After uptake of H₂ (3 equiv.), the catalyst was filtered off and the filtrate was evaporated, yielding 3 g of intermediate 11.

c) Preparation of intermediate 12 benzoic acid, 3-[[5-cyano-2-[[3-[[[(1,1-dimethylethoxy)carbonyl]amino]acetyl]amino]methyl]phenyl]amino]-4-pyrimidinyl]amino]-, 1,1-dimethylethyl ester

A mixture of intermediate 2 (0.0003 mol) and 3-chlorobenzenecarboperoxoic acid (0.00072 mol) in DCM (q.s.) was reacted for 2 hours, then intermediate 11 (0.00036 mol) was added and the reaction mixture was stirred for 1 hour at room temperature.
20 Finally, the mixture was heated to 60°C and the desired product was collected, yielding intermediate 12.

d) Preparation of intermediate 13 benzoic acid, 3-[[2-[[3-[[[(aminoacetyl)amino]methyl]phenyl]amino]-5-cyano-4-pyrimidinyl]amino]-

A mixture of intermediate 12 (0.03 mol) in 50% TFA in DCM (4 ml) was reacted for 1 hour at room temperature and then the solvent was evaporated, yielding intermediate 13.

Example A5

a) Preparation of intermediate 14 carbamic acid, [3-(2-methoxy-5-nitrophenoxy)propyl]-, 1,1-dimethylethyl ester

A mixture of 2-methoxy-5-nitro-phenol, (0.0766 mol), (3-bromopropyl)- carbamic acid, 1,1-dimethylethyl ester (0.092 mol) and potassium carbonate (0.092 mol) in DMF (130ml) was stirred at 60°C for 18 hours. Water was added. The mixture was extracted
5 with EtOAc/diethyl ether. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated till dryness. The crude crystals were taken up in diethyl ether/DIPE. The precipitate was filtered off and dried, yielding 24g (96%) of intermediate 14.

b) Preparation of intermediate 15 carbamic acid, [3-(5-amino-2-methoxyphenoxy)propyl]-, 1,1-dimethylethyl ester

A mixture of intermediate 14 (0.0735 mol) and Raney Nickel (20g) in MeOH (400ml)
10 was hydrogenated at room temperature for 2 hours under a 3 bar pressure, then filtered. The filtrate was evaporated till dryness, yielding 24.1g (>100%) of intermediate 15.

Example A6

a) Preparation of intermediate 16 L-proline, 1-[(4-chloro-5-fluoro-2-nitrophenyl)methyl]-, 1,1-dimethylethyl ester

A solution of L-proline, 1,1-dimethylethyl ester (0.010 mol) and 4-chloro-5-fluoro-2-nitrobenzaldehyde (0.010 mol) in DCM (30 ml) was cooled to 0°C and titanium tetrakis
15 (2-propanolato) (0.010 mol) was added, then the mixture was stirred for 1 hour at room temperature and NaBH(OAc)₃ (0.011 mol) was added. The reaction mixture was stirred for 3 hours at room temperature and extra titanium tetrakis (2-propanolato) (0.001 mol) and NaBH(OAc)₃ (0.001 mol) were added. After stirring for another 5 hours, water was
20 added and the mixture was filtered. The organic layer was separated, dried (K₂CO₃), and the solvent was evaporated, yielding intermediate 16 (S) (used as such in the next reaction step).

b) Preparation of intermediate 17 L-proline, 1-[(2-amino-4-chloro-5-fluorophenyl)methyl]-, 1,1-dimethylethyl ester

A mixture of intermediate 16 (0.009 mol) in EtOAc (150 ml) was hydrogenated with Pt/C 5% (1 g) as a catalyst in the presence of thiophene solution (1 ml). After uptake of
25 H₂ (3 equiv.), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by reversed phase high-performance liquid chromatography (NH₄OAc buffer), then the product fractions were collected and the organic component of the eluent was evaporated. The obtained precipitate was filtered off, washed with water and dried *in vacuo*, to give 1.1286 g (34 %) of intermediate 17.

c) Preparation of intermediate 18 L-proline, 1-[[4-chloro-2-[[5-cyano-2-(methylthio)-4-pyrimidinyl]amino]-5-fluorophenyl]methyl]-, 1,1-dimethylethyl ester

DIPEA (0.00026 mol) was added to a solution of 4-chloro-2-(methylthio)-5-pyrimidinecarbonitrile (0.00013 mol) and intermediate 17 (0.00014 mol) in 2-propanol (q.s.) and then the reaction mixture was stirred overnight at 60°C. LCMS monitoring indicated slow progression and the reaction had to be brought to 80°C for 27 hours to effect completion. Next, the solvent was evaporated, yielding intermediate 18 (used as such in the next reaction step). In another run intermediate 18 was isolated in 30% yield following reversed phase HPLC (NH₄OAc buffer), mp. 116.7-118.2 °C.

d) Preparation of intermediate 19 L-proline, 1-[[4-chloro-2-[[5-cyano-2-[[3-[3-[(1,1-dimethylethoxy)carbonyl]amino]propoxy]-4-methoxyphenyl]amino]-4-pyrimidinyl]amino]-5-fluorophenyl]methyl]-, 1,1-dimethylethyl ester

A solution of 3-chlorobenzenecarboxylic acid (0.000173 mol) in 1,2-dichloroethane (q.s.) was dried with anhydrous MgSO₄ and filtered, to give Residue I. Residue I was added to a solution of intermediate 18 (0.000157 mol) in 1,2-dichloroethane (q.s.) and the resulting mixture was stirred for 1 hour at room temperature. Upon addition of extra Residue I was added and the mixture was stirred for another 30 min. Intermediate 15 (0.000173 mol) was added and the reaction mixture was stirred overnight at 65°C. After cooling to room temperature, a saturated. NaHCO₃ soln. was added and the organic layer was separated and dried. Finally, the solvent was evaporated yielding intermediate 19, which was used as such in the next reaction step, (S).

e) Preparation of intermediate 20 L-proline, 1-[[2-[[2-[[3-(3-aminopropoxy)-4-methoxyphenyl]amino]-5-cyano-4-pyrimidinyl]amino]-4-chloro-5-fluorophenyl]methyl]- trifluoroacetic acid salt

A solution of intermediate 19 (0.000157 mol) in TFA/DCM (50/50) (5 ml) was reacted for 5 hours and then the solvent was evaporated at 30 °C, yielding intermediate 20 (S), isolated as a trifluoroacetic acid salt (used as such in the next reaction step).

Example A7

a) Preparation of intermediate 21 1-hexanol, 6-(4-chloro-2-nitrophenoxy)-, acetate (ester)

A solution of 4-chloro-2-nitrophenol (0.10 mol) in *N,N*-dimethylacetamide (200 ml) was treated for 15 minutes with potassium carbonate (17 g) at 90°C, then 6-bromo-1-hexanol, acetate (0.12 mol) was added at 60°C and the reaction mixture was stirred

overnight at 60°C. The mixture was poured out into ice-water (500 ml) and extracted with toluene (2 x 250 ml). The organic layers were combined, dried (MgSO₄), filtered off and the solvent was evaporated, yielding 42.3 g (> 100 %) of intermediate 21.

b) Preparation of intermediate 22 1-hexanol, 6-(2-amino-4-chlorophenoxy)-, acetate (ester)

- 5 A mixture of intermediate 21 (max. 0.11 mol) in THF (400 ml) was hydrogenated with Pt/C (5.0 g) as a catalyst in the presence of thiophene solution (3 ml). After uptake of H₂ (3 equiv.), the catalyst was filtered off and the filtrate was evaporated. The obtained residue was dissolved in DIPE (300 ml) and treated with 2-propanol/(6N HCl). After stirring for 1 hour, the resulting white solids were collected and dried, yielding 30.0 g of intermediate 22.

c) Preparation of intermediate 23 1-hexanol, 6-[4-chloro-2-[(6-chloro-4-pyrimidinyl)amino]phenoxy]-, acetate (ester)

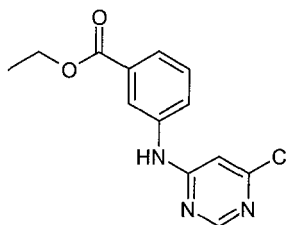
- 10 A mixture of 4,6-dichloropyrimidine (0.01 mol), intermediate 22 (0.012 mol) and DIPEA (0.025 mol) in EtOH (50 ml) was heated for 3 days on an oil bath at 80°C, then the solvent was evaporated and the obtained residue was purified by column chromatography. The desired product fractions were collected and the solvent was evaporated, yielding intermediate 23.

d) Preparation of intermediate 24 phenol, 5-[[6-[[5-chloro-2-[(6-hydroxyhexyl)oxy]phenyl]amino]-4-pyrimidinyl]amino]-2-methoxy-

- 15 A solution of intermediate 23 (0.0015 mol), 5-amino-2-methoxy-phenol (0.0015 mol) and HCl (cat. quant.) in butanol (50 ml) was stirred for 48 hours at reflux temperature and after completion, the solvent was evaporated under reduced pressure. The crude residue was filtered over silica gel (eluent: DCM/MeOH 92/8), then the desired product fractions were collected and the solvent was evaporated to dryness, yielding 0.300 g of intermediate 24.
- 20

Example A8

a) Preparation of intermediate 25



- 25 Ethyl 3-aminobenzoate (0.080 mol) was added to 2,4-dichloropyrimidine (0.066 mol) in isopropanol (80 ml), DIPEA (0.133 mol) was added. The reaction mixture was stirred and heated in the microwave for 3 hours at 160°C. The cooled reaction mixture was poured into a flask at room temperature, isopropanol (100 ml) was added, the

reaction mixture was stirred at room temperature. The crystallized solid was filtered and dried at 50°C under vacuum, yielding 11.3 g of intermediate 25, melting point 152°C.

b) Preparation of intermediate 26 benzoic acid, 3,3'-(4,6-pyrimidinediyl-diimino)bis-, ethyl ester, hydrochloric acid salt

To a solution of intermediate 25 (0.0072 mol) in isopropanol (50 ml), 3-aminobenzoic acid (0.0086 mol) was added. Hydrochloric acid in isopropanol (6N, 1.5 ml) was added. The reaction mixture was stirred and heated in the microwave for 2.5 hours at 130°C. The reaction mixture was concentrated, crystallized from acetonitrile/isopropanol. The precipitate was filtered off and dried at 50°C under vacuum, yielding 1.9 g of intermediate 26 isolated as a hydrochloric acid salt, melting point 248-250°C.

c) Preparation of intermediate 27 benzoic acid, 3-[[6-[[3-[[[6-[[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]amino]carbonyl]phenyl]amino]-4-pyrimidinyl]amino]-, ethyl ester

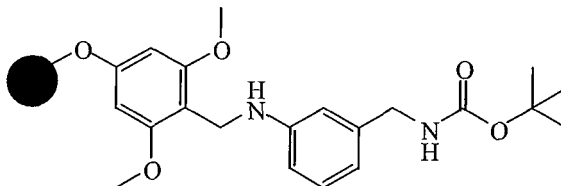
To a solution of intermediate 26 (1.32 mmol) in DCM (50 ml), *N*-Boc-1,6-hexanediamine (1.88 mmol) was added. 1-Hydroxybenzotriazole (1.88 mmol), *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.88 mmol), triethylamine (0.805 ml) was added. The reaction mixture was stirred for 48 hours at room temperature. A precipitate was formed in the reaction mixture. The solid was filtered and dried at 40°C under vacuum, yielding 430 mg of intermediate 27, melting point 163°C.

d) Preparation of intermediate 28 benzoic acid, 3-[[6-[[3-[[[6-aminohexyl]amino]carbonyl]phenyl]amino]-4-pyrimidinyl]amino]-, ethyl ester, trifluoroacetic acid salt

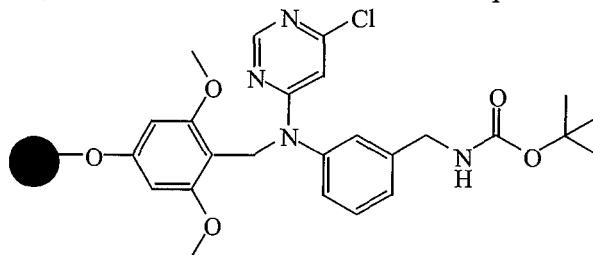
To a solution of intermediate 27 (0.69 mmol) in DCM (10 ml), a solution of 20% TFA in DCM was added. The reaction mixture was stirred for 1 hour at room temperature. The solvent was evaporated. toluene was added, the solvent was evaporated, ethanol was added. the solvent was evaporated. The product was used without further purification, yielding intermediate 28, isolated as a trifluoroacetic acid salt.

e) Preparation of intermediate 29 benzoic acid, 3-[[6-[[3-[[[6-aminohexyl]amino]carbonyl]phenyl]amino]-4-pyrimidinyl]amino]- Lithium charged

To a solution of intermediate 28 (0.69 mmol) in EtOH (20 ml), 1 ml water and LiOH (4.5 mmol) was added. The reaction mixture was stirred for 6.5 hours at 40°C. The solvent was evaporated. The product was used without further purification, yielding intermediate 29, isolated as Lithium charged.

Example A9a) Preparation of intermediate 30

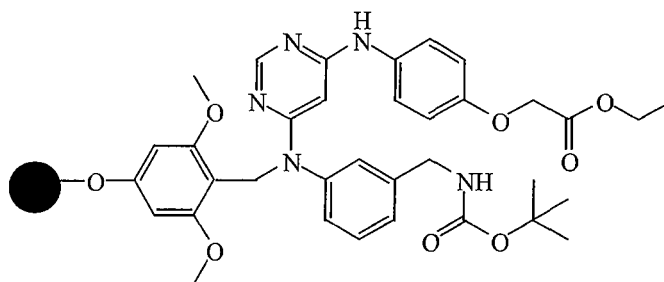
A mixture of Novabiochem 01-64-0261 commercial resin (2 g, loading : 0,94 mmol/g, 0.0018 mol) was washed with DCM (50 ml), then a solution of 3-tert-
5 butoxycarbonylaminomethylaniline (0.009 mol) in DCM/CH₃COOH 1% (25 ml) was added and the resulting mixture was shaken for 10 minutes at room temperature. Sodium triacetoxyborohydride (0.009 mol) was added, followed by addition of DCM/CH₃COOH 1% (25 ml) and the reaction mixture was shaken gently for 48 hours at room temperature. After filtration, the resin was washed 3 times with MeOH and 3
10 times with DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, yielding intermediate 30, which was used in next reaction step.

b) Preparation of intermediate 31

Intermediate 30 was washed with 1-butanol, to intermediate 30 was added 4,6-dichloropyrimidine (0.018 mol) and DIPEA (0.018 mol) in 1-butanol (50 ml). The reaction mixture was shaken for 40 hours at 90°C under N₂, then the resin was filtered
15 off and washed 3x with MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM.

This procedure was repeated: to intermediate 30 was added 4,6-dichloropyrimidine [1193-21-1] (0.018 mol) and DIPEA (0.018 mol) in 1-butanol (50 ml). The reaction mixture was shaken gently for 24 hours at 90°C, under N₂, then the resin was filtered
20 off and washed 3x with MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, yielding intermediate 31, which was used in next reaction step.

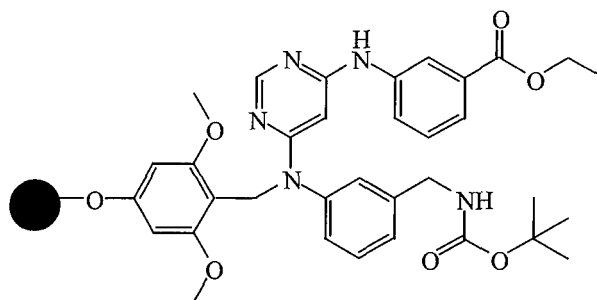
c) Preparation of intermediate 32



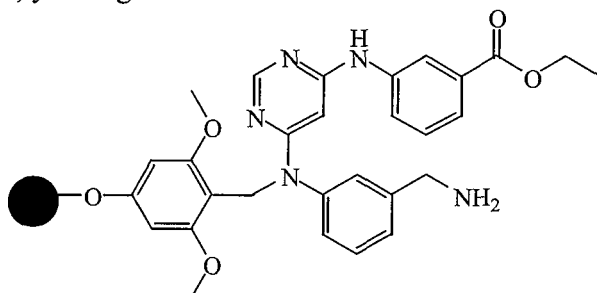
Intermediate 31 was washed with toluene, to intermediate 31 was added a mixture of ethyl (4-aminophenoxy)acetate (0.018 mol), Tris(dibenzylideneacetone)dipalladium(0) (0.00036 mol), (+/-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (0.0018 mol) and cesium carbonate (0.027 mol) in toluene (50 ml). The reaction was brought under
 5 nitrogen. The reaction mixture was shaken for 18 hours at 110°C, under N₂, then the resin was filtered off hot and washed 3 times with hot DMF (at 70°C), 3 times with hot water (at 50°C), 3 times with DMF and 3 times with water, 3 times with DMF and 3 times with water, 3 times with DMF and 3 times with DCM. Finally, washed 3 times with MeOH and 3 times with DCM, 3 times with MeOH and 3 times with DCM. The
 10 residue was dried under vacuum at 30°C, yielding intermediate 32.

d) Preparation of acetic acid, [4-[[[6-[[[3-(aminomethyl)phenyl]amino]-4-pyrimidinyl]amino]phenoxy]-

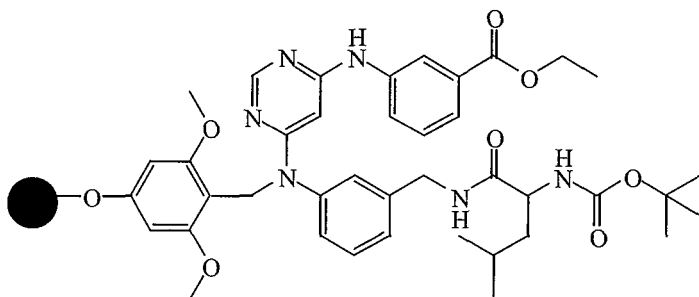
Intermediate 32 was washed with THF, to intermediate 32 (300mg) was added lithiumhydroxide (0.0049 mol) in THF (8 ml) and water (2 ml). The reaction mixture was shaken for 48 hours at 50°C, then the resin was filtered off and washed 3 times with water, 3 times with MeOH, 3 times with water and 3 times with DMF, 3 times
 15 with water and 3 times with DMF, 3 times with MeOH and 3 times with DCM, 3 times with MeOH and 3 times with DCM, 3 times with MeOH and 3 times with DCM. The residue was cleaved with TFA/TIS/DCM (25/2/73) for 4 hours, then the resin was filtered off and shaken for 1 hour with TFA/TIS/DCM (25/2/73). The resin was filtered off and washed 3 times with DCM. Finally, the combined solvents were blown dry
 20 under nitrogen at 50°C, 3 times DCM (5 ml) was added and blown dry under nitrogen at 50°C, yielding intermediate 33, isolated as a TFA-salt.

Example A10a) Preparation of intermediate 34

Intermediate 31 was washed with toluene, to intermediate 31 was added a mixture of ethyl 3-aminobenzoate (0.018 mol), Tris(dibenzylideneacetone)dipalladium(0) (0.00036 mol), (+/-)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene (0.0018 mol) and cesium carbonate (0.027 mol) in toluene (50 ml). The reaction was brought under nitrogen. The reaction mixture was shaken for 18 hours at 110 °C, under N₂, then the resin was filtered off hot and washed 3 times with hot DMF (at 70°C), 3 times with hot water (at 50°C), 3 times with DMF and 3 times with water, 3 times with DMF and 3 times with water, 3 times with DMF and 3 times with DCM. Finally, washed 3 times with MeOH and 3 times with DCM, 3 times with MeOH and 3 times with DCM. The residue was dried under vacuum at 30°C, yielding intermediate 34.

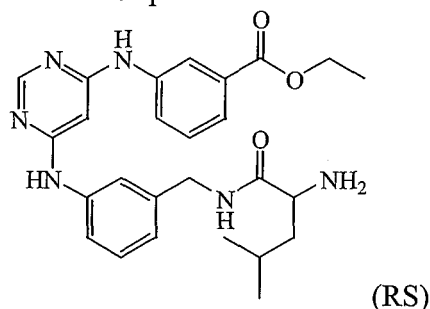
b) Preparation of intermediate 35

Intermediate 34 (400 mg) was washed with DCM, to intermediate 34 was added 10 ml of a solution of Trimethylsilyl trifluoromethanesulfonate / 2,6-lutidine (1M/1.5M) in DCM. The resin was shaken gently for 3 hours at room temperature. The resin was filtered, washed with 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, yielding intermediate 35, which was used in next reaction step.

c) Preparation of intermediate 36

Intermediate 35 was washed with DMF. To intermediate 35 was added a mixture of *N*-(tert-Butoxycarbonyl)-L-leucine (0.00108 mol), Fluoro-*N,N,N,N*-tetramethylformamidinium hexafluorophosphate (0.00108 mol) and DIPEA (0.0018 mol) in DMF (10 ml). The reaction mixture was shaken 48 hours at room temperature, then the resin was filtered off and washed with 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, 3x MeOH, 3x DCM, yielding (RS) intermediate 36, which was used in next reaction step.

d) Preparation of intermediate 37



Intermediate 36 was washed with THF, intermediate 36 was added lithiumhydroxide (0.0049 mol) in THF (8 ml) and water (2 ml). The reaction mixture was shaken for 48 hours at 50°C, then the resin was filtered off and washed 3 times with water, 3 times with MeOH, 3 times with water and 3 times with DMF, 3 times with water and 3 times with DMF, 3 times with MeOH and 3 times with DCM, 3 times with MeOH and 3 times with DCM, 3 times with MeOH and 3 times with DCM. The resin was cleaved with TFA/TIS/DCM (25/2/73) for 4 hours, then the resin was filtered off and shaken for 1 hour with TFA/TIS/DCM (25/2/73). The resin was filtered off and washed 3 times with DCM. Finally, the combined solvents were blown dry under nitrogen at 50°C, 3 times DCM (5 ml) was added and blown dry under nitrogen at 50°C, yielding intermediate 37 (RS), isolated as a TFA-salt.

20 Example A11

a) Preparation of phenol, 5-[(6-chloro-4-pyrimidinyl)amino]-2-methoxy-
intermediates 38 and 39 Free base: intermediate 38
 .HCl: intermediate 39

A solution of 4,6-dichloropyrimidine (0.1 mol), 5-amino-2-methoxyphenol (0.1 mol) and DIPEA (0.2 mol) in 2-propanol (200 ml) was heated in a microwave oven (divided in 5 portions) for 30 minutes at 130°C. Then the solvent was evaporated and the obtained residue was stirred in acetonitrile. The resulting precipitate was filtered off, washed with acetonitrile/DIPE and dried (vac.) at 60°C, yielding 15.01 g (60%) of intermediate 38. If desired, the compound can be converted to the HCl salt by stirring

in 6 N HCl/2-propanol and collecting and drying the obtained precipitate, yielding intermediate 39.

b) Preparation of intermediate 40 benzenemethanol, 3-[[6-[(3-hydroxy-4-methoxyphenyl)amino]-4-pyrimidinyl]amino]-

A mixture of intermediate 39 (0.05 mol, HCl salt) and 3-aminobenzenemethanol (0.05 mol) in n-butanol (80 ml) was equally divided over 2 microwave reaction vessels and each reaction mixture was heated for 30 minutes at 130°C. Extra 3-aminobenzenemethanol (0.0025 mol) was then added to each vessel and the resulting mixtures were heated for another 20 minutes at 130°C. 2-propanol and 6 N HCl/2-propanol was added to the combined mixtures, after which they were stirred overnight. The formed precipitate was collected and purified by reversed-phase high-performance liquid chromatography (NH₄OAc buffer). After evaporation of the organic component of the eluent, a white precipitation was obtained, filtered off and dried in the oven, yielding 9.2444 g (55 %) of intermediate 40, melting point 232.0-232.1 °C.

c) Preparation of intermediate 41 carbamic acid, [2-[5-[[6-[[3-(hydroxymethyl)phenyl]amino]-4-pyrimidinyl]amino]-2-methoxyphenoxy]ethyl]-, 1,1-dimethylethyl ester

A suspension of intermediate 40 (0.0075 mol) and cesium carbonate (0.0375 mol) in DMF (50 ml) was stirred for 1 hour at room temperature. Then (2-bromoethyl)-carbamic acid, 1,1-dimethylethyl ester (0.0090 mol) was added and the reaction mixture was stirred overnight. Extra (2-bromoethyl)-carbamic acid, 1,1-dimethylethyl ester (0.14 g) was added and the resulting mixture was stirred at 50°C. After 9 hours, the solvent was evaporated and DCM and water were added. The mixture was extracted 2 times with DCM and the combined organic layers were dried (anhydrous K₂CO₃). The product was purified over a pad of silica gel (eluent: DCM/EtOAc 60/40 to 0/100). The product fractions were collected and the solvent was evaporated. The obtained residue was triturated with DIPE and after filtration the desired product was dried (vac.) at 60°C, yielding 2.92 g (81 %) of intermediate 41.

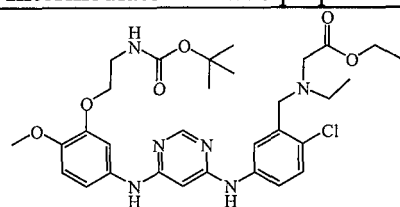
d) Preparation of intermediate 42 glycine, N-[[3-[[6-[[3-[2-[(1,1-dimethylethoxy)carbonyl]amino]ethoxy]-4-methoxyphenyl]amino]-4-pyrimidinyl]amino]phenyl]methyl]-N-methyl-, methyl ester

A suspension of intermediate 41 (0.0020 mol) and sodium iodide (0.0020 mol) in dry acetonitrile (50ml) was stirred at room temperature, then methanesulfonyl chloride (0.0024 mol) and DIPEA (0.060 mol) were added dropwise. After 15 minutes sarcosine methyl ester hydrochloride (0.0030 mol) was added. The reaction mixture was stirred for 16 hours at 65°C and, upon cooling to room temperature, PS-N=C=O (Aldrich, cat.

473685) (0.0030 mol) was added together with DCM (q.s.) and acetonitrile (q.s.). The mixture was shaken for 24 hours and then the resin was filtered off and washed with DCM, with MeOH, with DCM, with MeOH and with DCM again. The solvent was evaporated and the obtained residue was used as such in the next reaction step, yielding intermediate 42 .

5

Intermediate that was prepared according to Example A11d



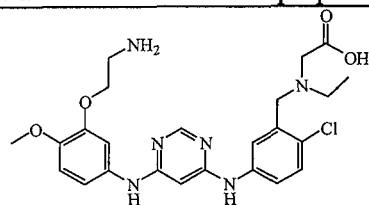
intermediate 94

e) Preparation of intermediate 43 glycine, N-[[3-[[6-[[3-[2-[(1,1-dimethylethoxy)carbonyl]amino]ethoxy]-4-methoxyphenyl]amino]-4-pyrimidinyl]amino]phenyl]methyl]-N-methyl-

Lithium hydroxide monohydrate (0.010 mol) was added to a solution of intermediate 42 (0.002 mol) in EtOH/water (8/2) (50 ml) and the reaction mixture was stirred overnight at 65°C. Extra lithium hydroxide monohydrate (0.010 mol) was added, then the mixture was stirred for 4 hours at 65°C and the solvent was evaporated to dryness, yielding intermediate 43, used as such in the next reaction step.

10

Intermediate that was prepared according to Example A11e



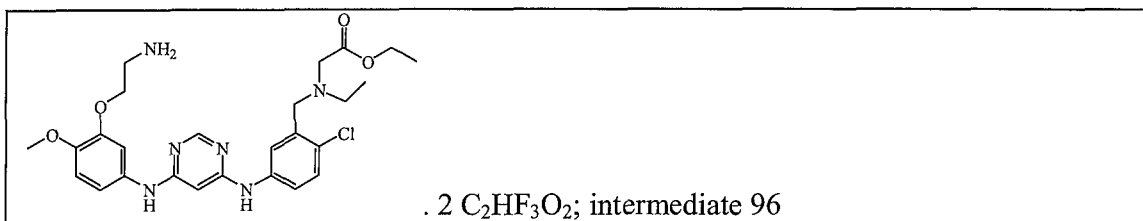
intermediate 95

f) Preparation of intermediate 44 glycine, N-[[3-[[6-[[3-(2-aminoethoxy)-4-methoxyphenyl]amino]-4-pyrimidinyl]amino]phenyl]methyl]-N-methyl- trifluoroacetic acid salt

A solution of intermediate 43 (0.002 mol) in TFA/DCM/TIS (49/49/2) (50 ml) was stirred for 1 hour at room temperature and then the solvent was evaporated, yielding intermediate 44, isolated as a trifluoroacetic acid salt, used as such in the next reaction step.

15

Intermediate that was prepared according to Example A11f



Example A12

a) Preparation of L-leucine, N-[(4-chloro-2-nitrophenyl)acetyl]-, 1,1-dimethylethyl ester
intermediate 45

A mixture of 4-chloro-2-nitro- benzeneacetic acid (0.0134 mol), L-leucine, 1,1-dimethylethyl ester, hydrochloride (0.0161 mol), triethylamine (0.0161 mol), EDC (0.0161 mol) and 1-hydroxy-1*H*-benzotriazole (0.0161 mol) in DCM/THF (60ml) was stirred at room temperature overnight, water was added then the mixture was extracted with DCM. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated till dryness. The residue (6.5g) was crystallized from EtOAc/DIPE. The precipitate was filtered, washed with DIPE and air dried, yielding 3.2g (63%) of intermediate 45.

b) Preparation of L-leucine, N-[(2-amino-4-chlorophenyl)acetyl]-, 1,1-dimethylethyl ester
intermediate 46

A mixture of intermediate 45 (0.0072 mol) and Pt/C 5% (0.28g) in thiophene solution 10% in EtOH (1.4ml) and THF (100ml) was hydrogenated at 50°C for 72 hours under a 3 bar pressure, then filtered over celite. The filtrate was evaporated. The residue (3.4g) was purified by column chromatography over silica gel (eluent: DCM/MeOH 100/0 to 98/2; 15-40μm). The pure fractions were collected and the solvent was evaporated, yielding 2g (77%) of intermediate 46 (L).

c) Preparation of L-leucine, N-[[4-chloro-2-[(6-iodo-4-pyrimidinyl)amino]phenyl]acetyl]-, 1,1-dimethylethyl ester
intermediate 47

A mixture of intermediate 46 (L) (0.0028 mol), 4,6-diiodo- pyrimidine (0.0056 mol) and DIPEA (0.0056 mol) in NMP (20ml) was heated in a microwaves (P=100W) at 170°C for 45 minutes, then cooled to room temperature, poured out into water and extracted with EtOAc/diethyl ether. The organic layer was washed with saturated NaCl, dried (MgSO₄), filtered, and the solvent was evaporated till dryness. The residue (4g) was purified by column chromatography over silica gel (eluent: DCM/MeOH 100/0 to 98/2; 15-40μm). The pure fractions were collected and the solvent was evaporated, yielding intermediate 47 (L).

d) Preparation of L-leucine, N-[[4-chloro-2-[[6-[[3-[[(1,1-dimethylethoxy)carbonyl]amino]propoxy]-4-

methoxyphenyl]amino]-4-pyrimidinyl]amino]phenyl]acetyl]-,
1,1-dimethylethyl ester

A mixture of intermediate 47 (L) (0.0017 mol), intermediate 15 (0.0021 mol) and HCl/2-propanol 5N (6 drops) in t-butanol (20ml) was stirred and refluxed for 18 hours, then cooled to room temperature, poured out into water and extracted with DCM. The organic layer was washed with potassium carbonate 10%, dried (MgSO₄), filtered, and the solvent was evaporated till dryness. The residue (1.46g) was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH₄OH 100/0/0 to 97/3/0.1; 15-40μm). The pure fractions were collected and the solvent was evaporated, yielding 0.54g (41%) of intermediate 48 (L).

e) Preparation of intermediate 49 L-leucine, N-[[2-[[6-[[3-(3-aminopropoxy)-4-methoxyphenyl]amino]-4-pyrimidinyl]amino]-4-chlorophenyl]acetyl]- trifluoroacetic acid salt

A mixture of intermediate 48 (L) (0.0007 mol) in TFA (2ml) and DCM (10ml) was stirred at room temperature for 18 hours. The solvent was evaporated till dryness, yielding intermediate 49, isolated as a trifluoroacetic acid salt. This product was used directly in the next reaction step.

Example A13

a) Preparation of intermediate 50 carbamic acid, (5-chloro-2-hydroxyphenyl)-, 1,1-dimethylethyl ester

A solution of di-*tert*-butyl dicarbonate ester (0.0696 mol) in THF (50ml) was added at 0°C to a solution of 2-amino-4-chlorophenol (0.0697 mol) in THF (100ml). The mixture was stirred at room temperature for 1 hour, then left at room temperature for 48 hours and evaporated in vacuo. The residue was purified by column chromatography over silica gel (eluent: DCM 100). The pure fractions were collected and the solvent was evaporated., yielding 13.6g (80%) of intermediate 50.

b) Preparation of intermediate 51 carbamic acid, [2-(2-bromoethoxy)-5-chlorophenyl]-, 1,1-dimethylethyl ester

A mixture of intermediate 50 (0.0615 mol), 1,2-dibromoethane (0.0313 mol) and cesium carbonate (0.0615 mol) in DMF (150ml) was stirred at room temperature for 48 hours, then poured out into water and extracted three times with diethyl ether and brine. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated in vacuo, yielding intermediate 51. This product was used directly in the next reaction step.

c) Preparation of intermediate 52 carbamic acid, [5-chloro-2-[2-[(3-hydroxypropyl)amino]ethoxy]phenyl]-, 1,1-dimethylethyl ester

A mixture of intermediate 51 (0.0615 mol) and 3-amino-1-propanol (0.612 mol) in EtOH (300ml) was stirred and refluxed for 48 hours, then condensed in vacuo, poured out into water and extracted three times with DCM. The organic phase was separated, washed with brine, dried (MgSO₄), filtered, and the solvent was evaporated in vacuo.

- 5 The residue was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH₄OH 95/5/0.5). The pure fractions were collected and the solvent was evaporated, yielding 6.4g (30%) of intermediate 52.

d) Preparation of intermediate 53 carbamic acid, [2-[4-chloro-2-[(1,1-dimethylethoxy)carbonyl]amino]phenoxy]ethyl](3-hydroxypropyl)-, phenylmethyl ester

- A solution of benzyl chloroformate (0.022 mol) in DCM (10ml) was added at 0°C to a mixture of intermediate 52 (0.0183 mol) and triethylamine (0.0226 mol) in DCM
10 (200ml). The mixture was stirred at room temperature overnight and was poured out into water. NaHCO₃ (50 ml) was added. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography over silica gel (eluent: DCM/MeOH 100/0 to 98/2). The pure fractions were collected and the solvent was evaporated, yielding 8.2g (94%) of
15 intermediate 53.

e) Preparation of intermediate 54 acetic acid, trifluoro-, 3-[[2-(2-amino-4-chlorophenoxy)ethyl][(phenylmethoxy)carbonyl]amino]propyl ester

TFA (15ml) was added at 0°C to a stirring mixture of intermediate 53 (0.0173 mol) in DCM (100ml) and the resulting reaction mixture was stirred for 16 hours at room temperature, then evaporated in vacuo, yielding 8.2g (99%) of intermediate 54. This product was used directly in the next reaction step.

f) Preparation of intermediate 55 carbamic acid, [2-[4-chloro-2-[[6-[(3-hydroxy-4-methoxyphenyl)amino]-4-pyrimidinyl]amino]phenoxy]ethyl](3-hydroxypropyl)-, phenylmethyl ester

- 20 A mixture of intermediate 38 (0.019 mol), intermediate 54 (0.017 mol) and HCl/2-propanol (20 drops, 5M) in 2-methyl-2-pentanol (25ml) was stirred and refluxed for 20 hours, then evaporated in vacuo. The residue was dissolved in DCM. TFA was added. The mixture was stirred overnight. TFA was added. The mixture was stirred at room temperature for 3 days, then evaporated in vacuo. The residue was dissolved in EtOH.
25 Potassium hydroxide (30 ml, 2M solution) was added. The mixture was stirred and refluxed, then evaporated in vacuo. HCl 3N was added to neutralize the mixture then water (200 ml) was added. The mixture was extracted three times with DCM. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated.

The residue was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH₄OH 97/3/0.1). The pure fractions were collected and the solvent was evaporated, yielding 8.3g (73%) of intermediate 55.

g) Preparation of intermediate 56 phenol, 5-[[6-[[5-chloro-2-[2-[(3-hydroxypropyl)amino]ethoxy]phenyl]amino]-4-pyrimidinyl]amino]-2-methoxy-

- A mixture of intermediate 55 (0.013 mol) in potassium hydroxide 40% (0.3ml) and EtOH (2ml) was stirred and refluxed for 1 hour. A solution of NH₄Cl was added. The solvent was removed in vacuo. The mixture was partitioned between DCM and saturated NaCl. The insoluble material was removed by filtration, dissolved in a mixture of CH₂Cl₂/MeOH/NH₄OH (80/20/3), filtered on a cake of silica and concentrated in vacuo. The residue was suspended in CH₂Cl₂ (200 ml) and DIEA (20 ml) was added. The mixture was stirred 16 hours at room temperature, then water (200 ml) was added. The organic extract was dried (MgSO₄) then concentrated in vacuo to yield 3.9g of intermediate 56, melting point 170°C.

Example A14

Preparation of intermediate 57 benzoic acid, 3-[(6-chloro-4-pyrimidinyl)amino]-, 1,1-dimethylethyl ester

- A mixture of 4,6-dichloropyrimidine (0.0168 mol), 3-aminobenzoic acid, 1,1-dimethylethyl ester (0.034 mol) and DIPEA (0.034 mol) in 2-propanol (60 ml) was reacted overnight at 90°C and then the solvent was evaporated. The residue was treated with 1N HCl and washed 3 times and then the organic solvent was evaporated. The obtained product was dissolved in DCM and washed 3 times with 1N HCl. The organic layer was separated, dried (MgSO₄) and the solvent was evaporated, yielding 5.61 g of intermediate 57.

Example A15

a) Preparation of intermediate 58 carbamic acid, [2-[[4-methoxy-3-nitrophenyl)methyl]amino]ethyl]-, 1,1-dimethylethyl ester

- A mixture of 4-methoxy-3-nitro- benzaldehyde (0.00625 mol) and (2-aminoethyl)- carbamic acid, 1,1-dimethylethyl ester (0.00625 mol) in MeOH (30 ml) was reacted for 2 hours at room temperature, then sodium tetrahydroborate (0.0069 mol) was added and the reaction mixture was stirred overnight. Water was added and the resulting mixture was extracted 3 times with toluene. The organic layer was separated, dried (MgSO₄) and the solvent was evaporated, yielding intermediate 58.

b) Preparation of carbamic acid, [2-[[3-amino-4-

intermediate 59 methoxyphenyl)methyl]amino]ethyl]-, 1,1-dimethylethyl ester

A mixture of intermediate 58 (0.001 mol) in MeOH (q.s.) was hydrogenated with Pd/C (0.1 g) as a catalyst in the presence of thiophene solution (0.1 ml). After uptake of H₂ (3 equiv.), the catalyst was filtered off and the filtrate was evaporated. After extraction with DCM, the organic layer was separated, dried (MgSO₄) and the solvent was

5 evaporated (vac.), yielding 1.579 g of intermediate 59.

c) Preparation of benzoic acid, 3-[[[6-[[[5-[[[2-[[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]amino]methyl]-2-methoxyphenyl]amino]-4-pyrimidinyl]amino]-, 1,1-dimethylethyl ester

A mixture of intermediate 59 (0.00305 mol), intermediate 57 (0.00254 mol), 2-methyl-2-propanol, sodium salt (0.00305 mol), tris(dibenzylideneacetone)dipalladium(0) (0.00013 mol) and BINAP (0.00026 mol) in toluene (40 ml) was reacted overnight at 90°C, then the solvent was evaporated and the residue was purified by reversed-phase high-performance liquid chromatography. The desired product fraction was collected and extracted, yielding 0.122 g of intermediate 60.

high-performance liquid chromatography. The desired product fraction was collected and extracted, yielding 0.122 g of intermediate 60.

d) Preparation of benzoic acid, 3-[[[6-[[5-[[[2-[[[(1,1-dimethylethoxy)carbonyl]amino]ethyl][(9H-fluoren-9-ylmethoxy)carbonyl]amino]methyl]-2-methoxyphenyl]amino]-4-pyrimidinyl]amino]-, 1,1-dimethylethyl ester

A mixture of intermediate 60 (0.00021 mol) and 1-[[*(9H*-fluoren-9-ylmethoxy)carbonyl]oxy]-2,5-pyrrolidinedione (0.00024 mol) in DCM (10 ml) was reacted for 3 hours at room temperature and then the reaction mixture was treated with an aq. NaHCO₃ soln. The organic layer was separated, dried (MgSO₄) and the solvent was evaporated, yielding 0.169 g of intermediate 61, used as such in the next reaction step).

15 an aq. NaHCO_3 soln. The organic layer was separated, dried (MgSO_4) and the solvent was evaporated, yielding 0.169 g of intermediate 61, used as such in the next reaction step).

e) Preparation of intermediate 62

benzoic acid, 3-[[6-[[5-[(2-aminoethyl)[(9H-fluoren-9-ylmethoxy)carbonyl]amino]methyl]-2-methoxyphenyl]amino]-4-pyrimidinyl]amino]-

A mixture of intermediate 61 (0.00021 mol) in TFA (50% in DCM) (5 ml) was reacted for 5 hours at room temperature and then the solvent was evaporated, yielding

20 intermediate 62.

Example A16

a) Preparation of phenylalanine, N-[[3-[[6-[[3-[2-[[[(1,1-dimethylethoxy)carbonyl]amino]ethoxy]-4-methoxyphenyl]amino]-4-pyrimidinyl]amino]phenyl]methyl]-, intermediate 63

methyl ester

Methanesulfonyl chloride (0.0006 mol) was added to a suspension of intermediate 41 (0.0005 mol) and sodium iodide (0.0005 mol) in acetonitrile (15 ml). Then DIPEA (0.0015 mol) was added and the reaction mixture was stirred for 15 minutes at room temperature. Next, phenylalanine methyl ester hydrochloride (q.s.) was added and the resulting mixture was stirred for 19 hours at 65°C. LCMS monitoring showed slow progression and the reaction had to be warmed to 80°C for 9 more hours to effect completion. After cooling to room temperature, DCM was added in the same quantity, then PS-benzaldehyde (Argonaut Technologies, cat. 800361) (0.003 mol) was added and the reaction mixture was shaken for 40 hours at room temperature. The resin was filtered off and then washed with DCM, with heptane, with DCM, with heptane again and finally with DCM again, yielding intermediate 63 (used as such in the next reaction step).

b) Preparation of phenylalanine, N-[[3-[[6-[[3-(2-aminoethoxy)-4-methoxyphenyl]amino]-4-pyrimidinyl]amino]phenyl]methyl]-
intermediate 64

A solution of intermediate 63 (0.0005 mol) in HCl 6 N (10 ml) and dioxane (10 ml) was stirred for 48 hours at 65°C. Since LCMS monitoring showed slow progression, the solvent was concentrated, HCl (37 %) was added and the resulting mixture was stirred again overnight at 65°C to effect completion. Finally, the solvent was evaporated, yielding intermediate 64 (RS), which was used as such in the next reaction step.

20 Example A17

Preparation of intermediate 65 phenol, 5-amino-2-(2-methoxyethoxy)-

A mixture of 2-(2-methoxyethoxy)-5-nitrophenol (0.0356 mol) and Raney Nickel (7.6g) in MeOH (150ml) was hydrogenated at room temperature for 6 hours under a 3 bar pressure, then filtered. The filtrate was evaporated till dryness, yielding 6.5g (100%) of intermediate 65.

25

Example A18

a) Preparation of 1-pentanol, 5-[[4-chloro-5-fluoro-2-nitrophenyl]methyl]amino]-
intermediate 66

A mixture of 4-chloro-5-fluoro-2-nitrobenzaldehyde (0.0295 mol) and 5-amino-1-pentanol (0.0295 mol) in MeOH (100ml) was stirred at room temperature for 18 hours. NaBH₃CN (3ml) and acetic acid (100ml) were added. The mixture was stirred at room temperature overnight, then quenched with water, poured out into saturated NaHCO₃ and extracted with DCM. The organic layer was separated, dried (MgSO₄), filtered, and

the solvent was evaporated till dryness, yielding 7.5g (87%) of intermediate 66. This product was used directly in the next reaction step.

b) Preparation of intermediate 67 1-pentanol, 5-[[[4-chloro-5-fluoro-2-nitrophenyl)methyl]methylamino]-

A mixture of intermediate 66 (0.0179 mol), formaldehyde 37% aqueous (0.0447 mol) and formic acid (0.0447 mol) was stirred at 50°C for 3 hours, then cooled to room temperature and diluted in water. pH was adjusted to 7 with saturated NaHCO₃. The mixture was extracted with DCM. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated till dryness, yielding 4.1g (75%) of intermediate 67.

c) Preparation of intermediate 68 1-pentanol, 5-[[[2-amino-4-chloro-5-fluorophenyl)methyl]methylamino]-

A mixture of intermediate 67 (0.0135 mol), iron (0.0673 mol) and ammonium chloride (0.135 mol) in THF/MeOH/water (400ml) was stirred and refluxed for 18 hours, then cooled to room temperature and filtered. The filtrate was diluted in DCM and washed with potassium carbonate 10%. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated till dryness. The residue (3.5g) was purified by column chromatography DCM/MeOH/NH₄OH 95/5/0.1; 70-200µm). The pure fractions were collected and the solvent was evaporated, yielding 1.2g (32%) of intermediate 68.

d) Preparation of intermediate 69 1-pentanol, 5-[[[4-chloro-2-[(6-chloro-4-pyrimidinyl)amino]-5-fluorophenyl)methyl]methylamino]-

A mixture of intermediate 68 (0.0043 mol), 4,6-dichloropyrimidine (0.0087 mol) and DIPEA (0.0096 mol) in NMP (25ml) was stirred at 170°C for 1 hour, then cooled to room temperature, poured out into water and extracted three times with diethyl ether. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH₄OH 98/2/1; 15-40µm). The pure fractions were collected and the solvent was evaporated, yielding 1.3g (77%) of intermediate 69.

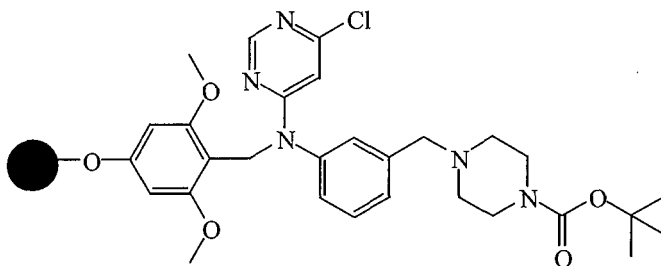
e) Preparation of intermediate 70 phenol, 5-[[[6-[[5-chloro-4-fluoro-2-[(5-hydroxypentyl)methylamino]methyl]phenyl]amino]-4-pyrimidinyl]amino]-2-(2-methoxyethoxy)-

A mixture of intermediate 69 (0.0033 mol), intermediate 65 (0.0039 mol) and HCl/2-propanol 5N (3 drops) in t-butanol (25ml) was refluxed for 16 hours, then evaporated till dryness. The residue was dissolved in 2-methyl-2-pentanol (15ml). The mixture was stirred and refluxed overnight, then cooled to room temperature, poured out into saturated NaHCO₃ and extracted with DCM. The organic layer was separated, dried

(MgSO₄), filtered, and the solvent was evaporated till dryness. The crude oil (1.7g) was crystallized from DCM/MeOH (95/5). The precipitate was filtered off and dried, yielding 0.46g (25%) of intermediate 70.

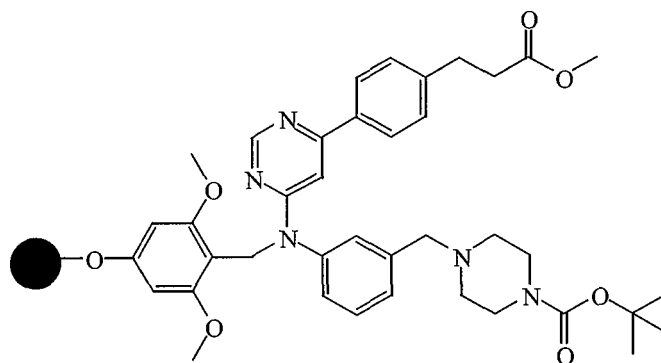
5 Example A19

a) Preparation of intermediate 71



Intermediate 71 was prepared in exact the same manner as intermediate 31, only as starting material 3-(1-Boc-piperazin-4-yl-methyl)-aniline [361345-40-6] was used in the synthesis.

b) Preparation of intermediate 72



- 10 Intermediate 71 was washed with dioxane. To intermediate 71 (400 mg) was added a mixture of [4-(2-methoxycarbonyl)phenyl]boronic acid (0.0018 mol), tris(dibenzylideneacetone)dipalladium(0) (0.000036 mol), 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium chloride (0.000036 mol) and cesium carbonate (0.0036 mol) in dioxane (10 ml). The reaction was brought under nitrogen.
- 15 The reaction mixture was shaken for 18 hours at 90°C, under N₂, then the resin was filtered off hot and washed 3 times with hot DMF (at 70°C), 3 times with hot water (at 50°C), 3 times with DMF and 3 times with water, 3 times with DMF and 3 times with DCM. Finally, washed 3 times with MeOH and 3 times with DCM, 3 times with MeOH and 3 times with DCM, yielding intermediate 72, which was used in next
- 20 reaction step.

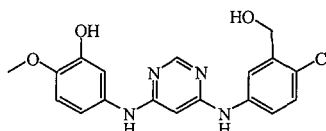
c) Preparation of intermediate 73

benzenepropanoic acid, 4-[6-[[3-(1-piperazinylmethyl)phenyl]amino]-4-pyrimidinyl]-

Intermediate 72 was washed with THF, to intermediate 72 was added lithiumhydroxide (0.0049 mol) in THF (8 ml) and water (2 ml). The reaction mixture was shaken for 48 hours at 50°C, then the resin was filtered off and washed 3 times with water, 3 times with MeOH, 3 times with water and 3 times with DMF, 3 times with water and 3 times with DMF, 3 times with MeOH and 3 times with DCM, 3 times with MeOH and 3 times with DCM, 3 times with MeOH and 3 times with DCM. The resin was cleaved with TFA/TIS/DCM (25/2/73) for 4 hours, then the resin was filtered off and shaken for 1 hour with TFA/TIS/DCM (25/2/73). The resin was filtered off and washed 3 times with DCM. Finally, the combined solvents were blown dry under nitrogen at 50°C, 3 times DCM (5 ml) was added and blown dry under nitrogen at 50°C, yielding intermediate 73 isolated as a TFA-salt.

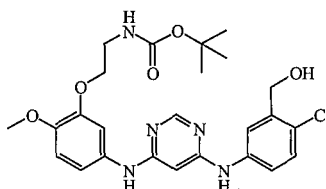
Example A20

a) Preparation of intermediate 74

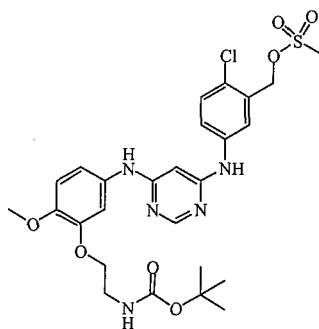


Intermediate 39 (0.027 mol) and 5-amino-2-chloro-benzenemethanol (0.032 mol) were dissolved in DMF (60 ml). The reaction solution was stirred and heated at 140°C for 5 hours, yielding intermediate 74, (mixture used in next reaction step, without further work-up/purification).

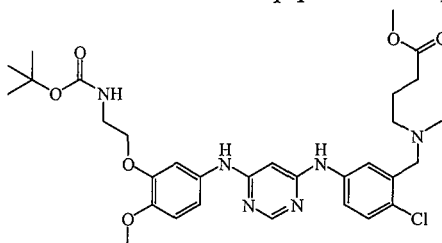
b) Preparation of intermediate 75



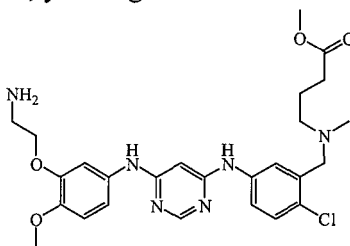
To intermediate 74 (crude reaction mixture containing max. 0.027 mol of intermediate) was added DMF (200 ml) and Cesium carbonate (0.162 mol). The resulting suspension was stirred for one hour at room temperature. Then (2-bromoethyl)-carbamic acid, 1,1-dimethylethyl ester (0.054 mol) was added and the reaction mixture was stirred for 24 hours at room temperature. The mixture was filtered through a fritted funnel. The filtrate's solvent was evaporated on the Rotavap. The residue (dark oil) was purified by column chromatography. The product fractions were collected and the solvent was evaporated, yielding 6.73 g (48%) of intermediate 75.

c) Preparation of intermediate 76

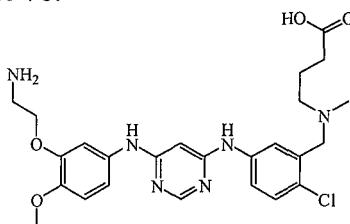
Intermediate 75 (0.001750 mol) was suspended in a mixture of DIPEA (0.00525 mol) and acetonitrile (33.5 ml). Methanesulfonyl chloride (0.002275 mol) was added and the resulting homogeneous solution was stirred for 30 minutes, yielding intermediate 76, (mixture used in next reaction step, without further work-up/purification).

d) Preparation of intermediate 77

- 5 4-(methylamino)- butanoic acid, methyl ester (0.000500 mol) and DIPEA (0.000750 mol) were added to intermediate 76 (± 0.000250 mol) in acetonitrile (5 ml) in a tube. The tube was capped with a silicon stopper and the reaction mixture was shaken for 24 hours at 65°C. The mixture was allowed to cool to room temperature, and diluted with 5 ml of DCM. Scavenger was added and the mixture was shaken overnight at room
- 10 temperature. The solvent was removed, yielding intermediate 77.

e) Preparation of intermediate 78

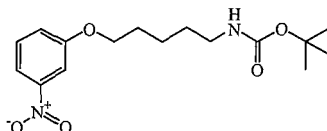
Intermediate 77 (± 0.000250 mol) was taken up into a mixture of TFA/DCM/TIS 49/49/2 v/v/v (5 ml). The reaction mixture was stirred overnight at room temperature. The solvent and excess of TFA was evaporated. The residue was dried (oil-pump vacuum; 65°C), yielding intermediate 78.

f) Preparation of intermediate 79

Intermediate 78 (± 0.000250 mol) was taken up into a mixture of THF/water 8/1 (10 ml). Lithium hydroxide monohydrate (0.00250 mol; 10 equiv) was added. The reaction mixture was stirred overnight at 65°C. The solvent was evaporated. The residue was dried (oil-pump vacuum). The residue was taken up into dry DMF (10 ml), filtered off,
5 then used as such in next reaction step, yielding intermediate 79.

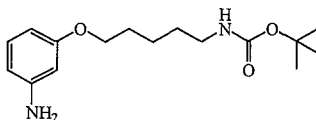
Example A21

a) Preparation of intermediate 80



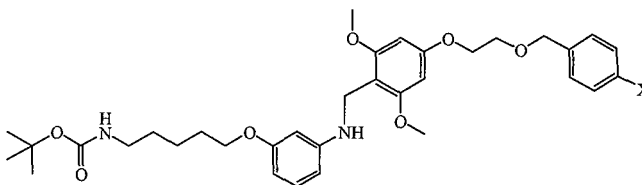
A mixture of (5-hydroxypentyl)- carbamic acid, 1,1-dimethylethyl ester (0.06 mol), 3-nitro- phenol (0.05 mol) and triphenylphosphine (0.05 mol) in THF (300 ml) was
10 stirred at 0°C and bis(1-methylethyl) diazenedicarboxylate (0.05 mol) was added dropwise at 0°C. The reaction mixture was stirred for 15 minutes at 0°C and was then allowed to reach room temperature. The mixture was stirred at ambient temperature for 1 hour and the solvent was evaporated. The residue was purified by short column chromatography (eluent: DCM). The product fractions were collected and the solvent
15 was evaporated. The obtained residue (12 g) was precipitated from petroleum benzin and the resulting precipitate was collected, yielding 9.3 g of intermediate 80, melting point 65°C.

b) Preparation of intermediate 81



A mixture of intermediate 80 (0.028 mol) in MeOH (250 ml) was hydrogenated at 50°C with Pd/C 10% (2 g) as a catalyst in the presence of thiophene solution (1 ml).
20 After uptake of H₂ (3 equiv.), the catalyst was filtered over dicalite and the filtrate was evaporated, yielding 9 g of intermediate 81.

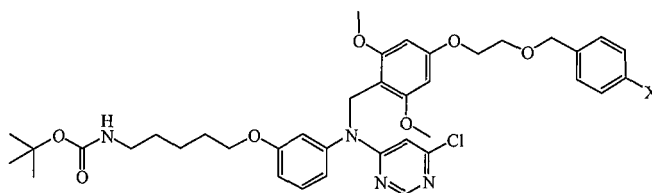
c) Preparation of intermediate 82



2-(3,5-Dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene (Novabiochem; 01-64-0261) (0.0018 mol) was washed with 1% acetic acid in DCM (50 ml), then a solution of intermediate 81 (0.009 mol) in 1% acetic acid in DCM (25 ml) was added and the
25 resulting mixture was shaken for 10 minutes at room temperature. Tris(acetato- α -O)-hydroborate (1-), sodium (0.009 mol) was added, followed by addition of 1% acetic acid in DCM (25 ml) and the reaction mixture was shaken for 2 days at room

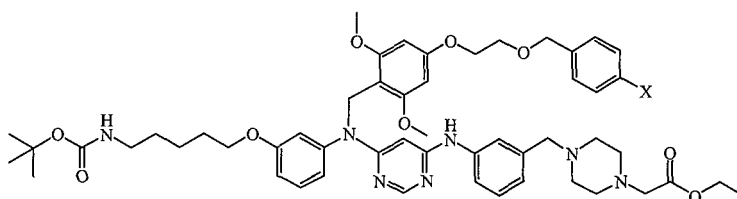
temperature. After filtration, the resin was washed 4 x [3 times with MeOH and 3 times with DCM], yielding intermediate 82.

d) Preparation of intermediate 83



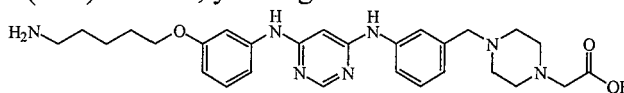
A mixture of intermediate 82 (max. 0.0018 mol; previously washed with butanol (q.s.)), 4,6-dichloro- pyrimidine (0.018 mol) and DIPEA (0.018 mol) in butanol (50 ml) was shaken for 40 hours at 90°C and under N₂, then the resin was filtered off, yielding (without cleavage), intermediate 83.

e) Preparation of intermediate 84

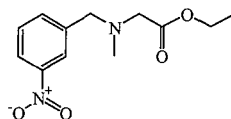


A mixture of intermediate 83 (max. 0.0018 mol; previously washed 2 x with toluene), 4-[(3-aminophenyl)methyl]- 1-piperazineacetic acid, ethyl ester (0.018 mol), Pd₂(dba)₃ [cas number 51364-51-3] (0.00036 mol), BINAP (0.0018 mol) and cesium carbonate (0.027 mol) in toluene (p.a., dry, 50 ml) was shaken for 18 hours at 110°C and under N₂, then the resin was filtered off hot and washed 3 times with hot DMF, 3 times with hot DMF/water, 3 x with hot DMF, 3 times with water and 3 times with DMF, 3 x with DCM, 3 x with DMF, washed 2 x [3 times with DCM and 3 times with MeOH], and 3 x with DCM. A sample was cleaved with TFA/TIS/DCM (25/2/73). After evaporation, the obtained residue was dried (vac.) at 30°C, yielding intermediate 84.

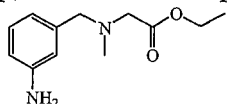
f) Preparation of intermediate 85



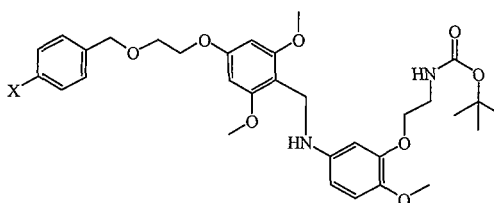
A mixture of intermediate 84 (0.4 g; max. 0.00018 mol) and lithium hydroxide monohydrate (0.0048 mol) in THF (8 ml) and water (2 ml) was shaken for 48 hours at 50°C, then the resin was filtered off, washed 3 times with water (50°C), 3 times with DMF, then 3 x with DCM. The reaction mixture was cleaved with TFA/TIS/DCM (25/2/73) over 4 hours, then filtered and the filtrate was collected. The resin was shaken again for 1 hour with TFA/TIS/DCM 25/2/73 , then filtered and the filtrate was collected. The filtrates were combined and the solvent was evaporated at 70°C under N₂ flow, yielding intermediate 85.

Example A22a) Preparation of intermediate 86

- N*-methyl- glycine, ethyl ester (0.326 mol) was added to a mixture of 3-nitro-benzaldehyde (0.326 mol) in 1,2-dichloro- ethane (1000 ml). 2-propanol, titanium(4+) salt (0.39 mol) was added and the reaction mixture was stirred for 10 minutes at room temperature. Tris(acetato- α -O) hydroborate (1-), sodium (0.82 mol) was added and the reaction mixture was stirred for 2 hours at room temperature under N₂ atmosphere. Water (500 ml) was added carefully. DCM (500 ml) was added. The biphasic mixture was filtered through dicalite. The filtrate was separated into it's layers. The organic phase was washed with water, dried (MgSO₄), filtered and the solvent was evaporated.
- The residue was concentrated with DIPE, then with toluene, yielding intermediate 86 (quantitative yield, used in next reaction step, without further purification).

b) Preparation of intermediate 87

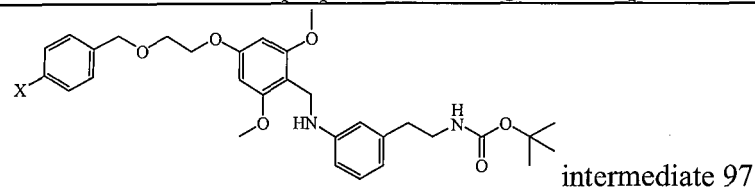
- A mixture of intermediate 86 (max. 0.326 mol) in EtOH (600 ml) was hydrogenated at 50°C with Pd/C 10% (4 g) as a catalyst in the presence of thiophene solution (2 ml). After uptake of H₂ (3 equiv), the catalyst was filtered off over dicalite and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: DCM/MeOH 97/3). The product fractions were collected and the solvent was evaporated, yielding 44 g (58%) of intermediate 87.

Example A23a) Preparation of intermediate 88

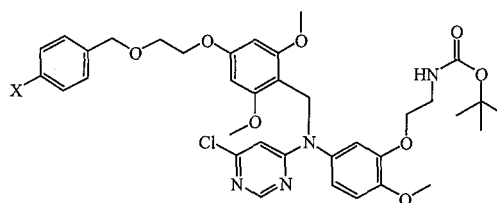
- 2-(3,5-Dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene (Novabiochem; 01-64-0261) (0.0018 mol) was washed with 1% acetic acid in DCM (50 ml), then a solution of [2-(5-amino-2-methoxyphenoxy)ethyl]- carbamic acid, 1,1-dimethylethyl ester (0.009 mol) in 1% acetic acid in DCM (25 ml) was added and the resulting mixture was shaken for 10 minutes at room temperature. Tris(acetato- α -O)-hydroborate (1-), sodium (0.009 mol) was added, followed by addition of 1% acetic acid in DCM (25 ml) and the reaction mixture was shaken over the weekend at room temperature. After filtration, the

resin was washed 4 x [3 times with MeOH and 3 times with DCM], yielding intermediate 88.

Intermediate that was prepared according to Example A23a

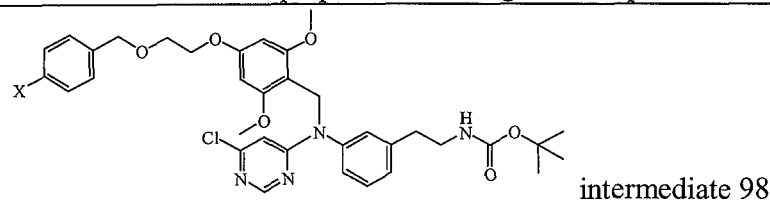


b) Preparation of intermediate 89

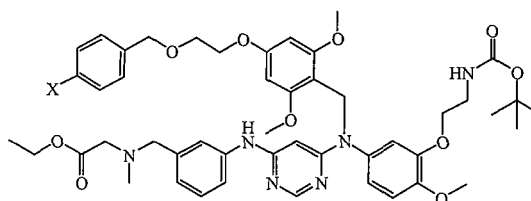


A mixture of intermediate 88 (max. 0.0018 mol; previously washed with butanol (q.s.)), 4,6-dichloro- pyrimidine (0.018 mol) and DIPEA (0.018 mol) in butanol (50 ml) was shaken for 40 hours at 90°C and under N₂, then the resin was filtered off and washed 4 x [3 times with DCM and 3 times with MeOH] and finally 3 times with DCM. A sample of the resin was cleaved with TFA/TIS/DCM (25/2/73) for 1 hour and then the solvent was evaporated, yielding intermediate 89.

Intermediate that was prepared according to Example A23b



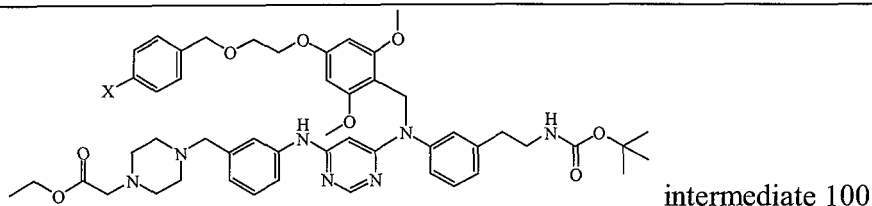
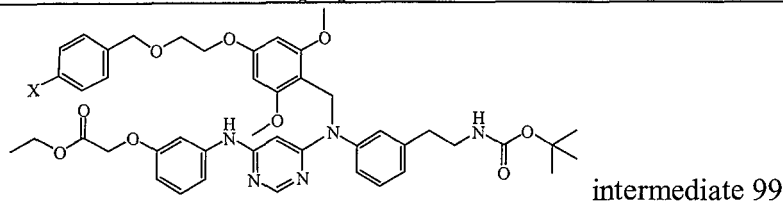
c) Preparation of intermediate 90



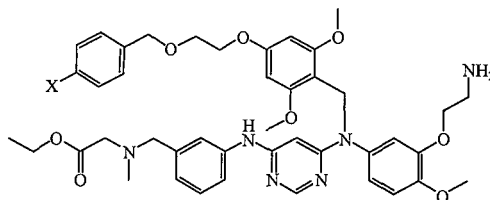
A mixture of intermediate 89 (max. 0.0018 mol), intermediate 87 (0.018 mol), Pd₂(dba)₃ [cas number 51364-51-3] (0.00036 mol), BINAP (0.0018 mol) and cesium carbonate (0.027 mol) in toluene (p.a., dry, 50 ml) was shaken for 18 hours at 110°C and under N₂, then the resin was filtered off hot and washed 3 times with hot DMF (at 70°C), 3 times with hot water (at 50°C), 2 x [3 times with DMF and 3 times with water], 3 times with DMF and 3 times with DCM. Finally, washed 2 x [3 times with MeOH and 3 times with DCM]. A sample was cleaved with TFA/TIS/DCM (25/2/73) and LCMS-analyses showed an impurity. The residue was washed again 5 x [3 times

with MeOH and 3 times with DCM], then a sample was cleaved with TFA/TIS/DCM (25/2/73). After evaporation, the obtained residue was dried (vac.) at 30°C, yielding intermediate 90.

Intermediates that were prepared according to Example A23c

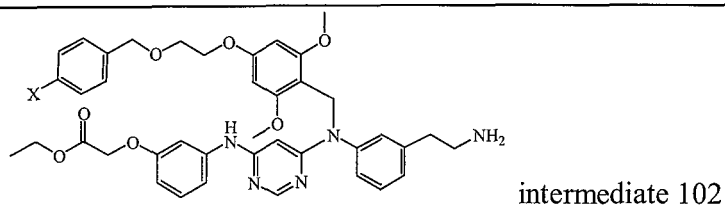
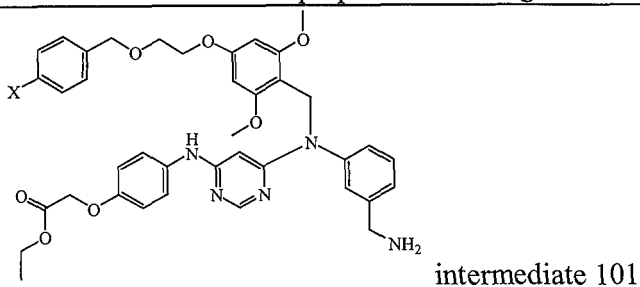


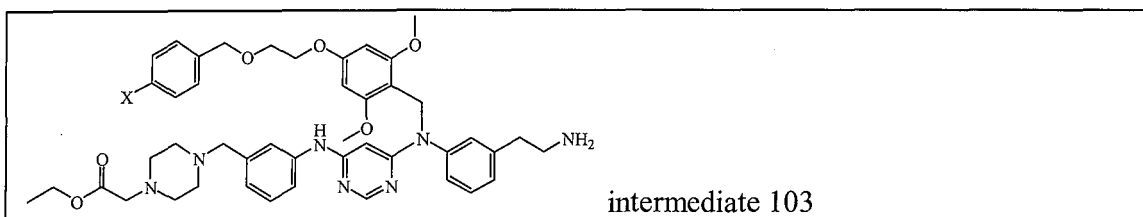
d) Preparation of intermediate 91



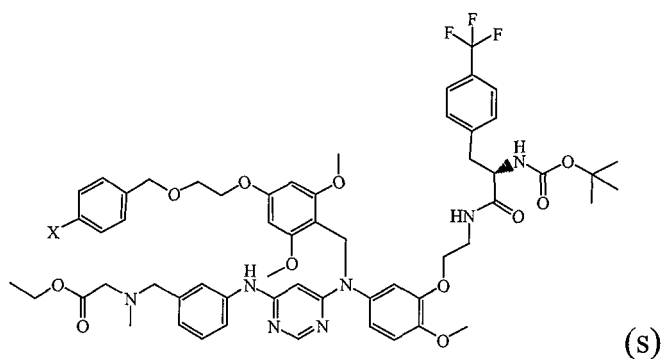
- 5 Intermediate 90 (0.400 g of crude resin, previously washed with DCM) was shaken in trifluoro- methanesulfonic acid, trimethylsilyl ester/2,6-dimethyl- pyridine/DCM (1.5 M/1 M/10 ml) for 4 hours at room temperature. The resin was filtered off, washed with DCM (1 x), MeOH (3 x), [DCM (3 x), MeOH (3 x)][4 x], washed with DCM (3 x), then dried, yielding intermediate 91.

Intermediates that were prepared according to Example A23d



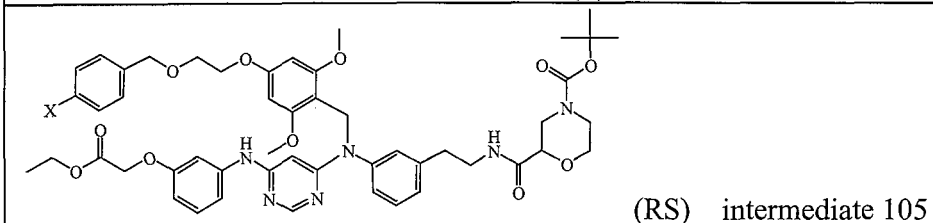
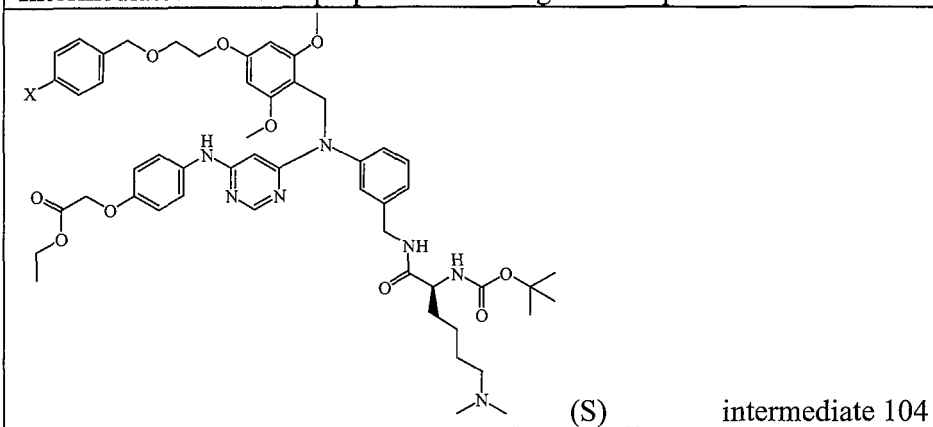


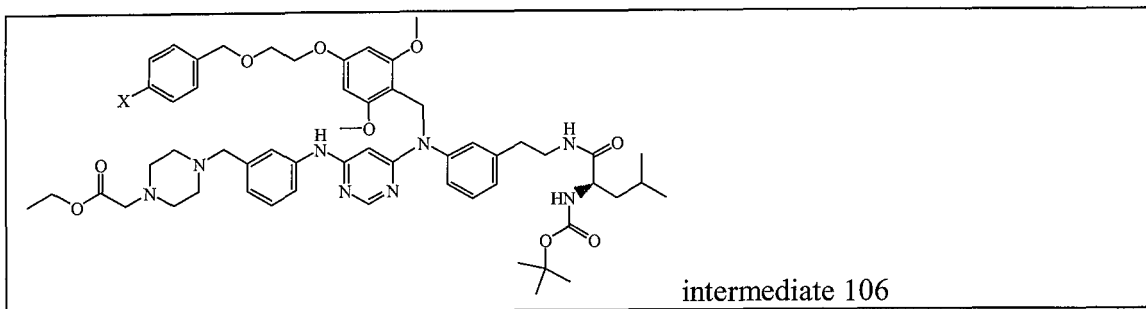
e) Preparation of intermediate 92



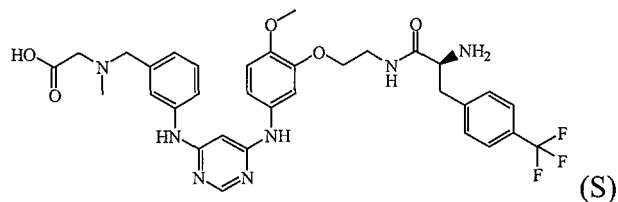
- A solution of *N*-(1,1-dimethylethoxy)carbonyl]-4-(trifluoromethyl)- L-phenylalanine (0.00108 mol), tetramethylfluoroformamidinium hexafluorophosphate (0.00108 mol) and DIPEA (0.0018 mol) in DMF dry (10 ml) was added to resin intermediate 91 (crude; previously washed 2 x with dry DMF) and the whole was shaken for 48 hours at room temperature. The resin was filtered off, washed with DCM (3 x), with [MeOH (3 x), DCM (3 x)] [5 x], then dried, yielding intermediate 92.

Intermediates that were prepared according to Example A23e





f) Preparation of intermediate 93



A mixture of intermediate 92 (crude, previously washed with THF) and lithium hydroxide monohydrate (0.0048 mol) in THF (8 ml) and water (2 ml) was shaken for 48 hours at 50°C, then the resin was filtered off, washed 3 times with water (50°C), 3 times with DMF (50°C), then 1 x with MeOH and 3 x with DCM. The reaction mixture was cleaved with TFA/TIS/DCM (25/2/73) over 4 hours, then filtered and the filtrate was collected. The resin was shaken again for 1 hour with TFA/TIS/DCM 25/2/73, then filtered and the filtrate was collected. The filtrates were combined and the solvent was evaporated at 50°C under N₂ flow. Acetonitrile was added to the residue, then concentrated again at 50°C (2 x), yielding intermediate 93.

[illegible]

B. Preparation of the final compoundsExample B1

Preparation of 14,19-dioxa-2,4,8,26-
compound 1 tetraazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacosa-
 1(24),3,5,7(26),9,11,13(25),16,20,22-decaene-6-carbonitrile, (16Z)-
 Grubbs' catalyst (0.00008 mol, Registry Number: 172222-30-9) was added to
 intermediate 1 (0.0006 mol) in DCM p.a. (200 ml). The reaction mixture was stirred for
 5 16 hours at 50°C. The solvent was evaporated under reduced pressure. The residue was
 purified by column chromatography. The product fractions were collected and the
 solvent was evaporated, yielding 0.0081 g of compound 1.

Example B2

Preparation of 14,19-dioxa-2,4,8,26-
compound 2 tetraazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacosa-
 1(24),3,5,7(26),9,11,13(25),20,22-nonaene-6-carbonitrile
 10 A solution of 2,4-dichloro-5-pyrimidinecarbonitrile (0.003 mol) in diglyme (100 ml)
 was added in one portion to a solution of 3,3'-[1,4-butanediylbis(oxy)]bis- benzenamine
 (0.003 mol) in diglyme (400 ml) at 90°C. The reaction mixture was stirred and refluxed
 for 16 hours and then cooled. The solvent was evaporated under reduced pressure and
 the residue was purified on a silica gel filter (eluent: DCM/MeOH 99.5/0.5). The
 15 product fractions were collected and the solvent was evaporated under reduced
 pressure. The residue was stirred in DCM/MeOH (98/2), the resulting precipitate was
 filtered off and dried, yielding 0.1806 g (16 %) of compound 2.

Example B3

Preparation of 18-oxa-2,4,8,15,25-
compound 3 pentaazatetracyclo[17.3.1.1~3,7~.1~9,13~]pentacosa-
 1(23),3,5,7(25),9,11,13(24),19,21-nonaene-6-carbonitrile, 14-oxo-
 20 A mixture of HBTU (0.0004 mol) in DMF extra dry (50 ml) was stirred under N₂ at
 room temperature, then a mixture of intermediate 5 (0.0004 mol) and DIPEA (0.004
 mol) in DMF extra dry (50 ml) was added dropwise over 1 hour and the reaction
 mixture was stirred overnight. The solvent was evaporated and the residue was stirred
 in boiling MeOH (10 ml) and water (5 ml). The mixture was allowed to cool under
 25 stirring and the resulting precipitate was filtered off. The filtrate was evaporated and
 the obtained residue was taken up in DCM/MeOH, then washed with 0.1N HCl and 2
 times with 0.1N NaOH. The organic layer was separated, dried, filtered off and the

- solvent was evaporated. The residue was purified by RediSep®-Flash column chromatography (eluent: DCM/(MeOH/NH₃) 99/1 to 97/3). The desired product fractions were collected and the solvent was evaporated. The residue was stirred in boiling acetonitrile, then the precipitate was filtered off and dried, yielding 0.022 g (15%) of compound 3, melting point > 260°C.

Compounds that were prepared according to Example B3	
21-oxa-2,4,8,15,28-pentaazatetracyclo[20.3.1.1~3,7~.1~9,13~]octacos-1(26),3,5,7(28),9,11,13(27),22,24-nonaene-6-carbonitrile, 14-oxo-	Compound 18 mp. > 260 °C
14-oxa-2,4,8,19,27-pentaazatetracyclo[19.3.1.1~3,7~.1~9,13~]heptacos-1(25),3,5,7(27),9,11,13(26),21,23-nonaen-20-one	Compound 19
14-oxa-2,4,8,17,25-pentaazatetracyclo[17.3.1.1~3,7~.1~9,13~]pentacos-1(23),3,5,7(25),9,11,13(24),19,21-nonaene-6-carbonitrile, 18-oxo-	Compound 20 mp. > 260 °C
14-oxa-2,4,8,21,29-pentaazatetracyclo[21.3.1.1~3,7~.1~9,13~]nonacos-1(27),3,5,7(29),9,11,13(28),23,25-nonaen-22-one	Compound 21 mp. 262 °C
14-oxa-2,4,8,20,28-pentaazatetracyclo[20.3.1.1~3,7~.1~9,13~]octacos-1(26),3,5,7(28),9,11,13(27),22,24-nonaen-21-one	Compound 22 mp. >260 °C
18-oxa-2,4,8,15,25-pentaazatetracyclo[17.3.1.1~3,7~.1~9,13~]pentacos-1(23),3,5,7(25),9,11,13(24),19,21-nonaen-16-one	Compound 23 mp. >260 °C
2,4,8,15,23-pentaazatetracyclo[15.3.1.1~3,7~.1~9,13~]tricos-1(21),3,5,7(23),9,11,13(22),17,19-nonaen-16-one	Compound 24 mp. >250 °C

Example B4

Preparation of compound 4 14,22-dioxa-2,4,8,19,29-pentaazatetracyclo[21.3.1.1~3,7~.1~9,13~]nonacos-1(27),3,5,7(29),9,11,13(28),23,25-nonaen-20-one

- A mixture of intermediate 9 (0.0023 mol) and DIPEA (0.0057 mol) in DMF (100 ml) was added dropwise to a mixture of HBTU (0.0057 mol) in DMF (200 ml) at room temperature and then the reaction mixture was stirred for 2 hours at room temperature. The solvent was evaporated and the obtained residue was dissolved in DCM/MeOH (8/2) (500 ml). This solution was washed with water, then the organic layer was separated, dried (MgSO₄), filtered off and the solvent was evaporated. The residue was purified by reversed-phase high-performance liquid chromatography (Standard method,

- gradient eluent). The product fractions were collected and the solvent was evaporated. The residue was dissolved in DCM and washed with water. The organic layer was separated, dried (MgSO₄), filtered off and the solvent was evaporated. The residual fraction was crystallised from acetonitrile, then the precipitate was filtered off, washed with a small amount of acetonitrile and dried (vac.), yielding 0.085 g (9 %) of compound 4.

Compounds that were prepared according to Example B4	
14,21-dioxa-2,4,8,17,28-pentaazatetracyclo[20.3.1.1~3,7~.1~9,13~]octacosal(26),3,5,7(28),9,11,13(27),22,24-nonaene-6-carbonitrile, 16-oxo-	Compound 25 mp. > 260 °C
14,22-dioxa-2,4,8,17,29-pentaazatetracyclo[21.3.1.1~3,7~.1~9,13~]nonacosal(27),3,5,7(29),9,11,13(28),23,25-nonaene-6-carbonitrile, 16-oxo-	Compound 26 mp. > 260 °C
14,20-dioxa-2,4,8,17,27-pentaazatetracyclo[19.3.1.1~3,7~.1~9,13~]heptacosal(25),3,5,7(27),9,11,13(26),21,23-nonaene-6-carbonitrile, 16-oxo-	Compound 27 mp. 260 °C
14,21-dioxa-2,4,8,18,28-pentaazatetracyclo[20.3.1.1~3,7~.1~9,13~]octacosal(26),3,5,7(28),9,11,13(27),22,24-nonaene-6-carbonitrile, 19-oxo-	Compound 28 mp. 236 °C
14,21-dioxa-2,4,8,18,28-pentaazatetracyclo[20.3.1.1~3,7~.1~9,13~]octacosal(26),3,5,7(28),9,11,13(27),22,24-nonaen-19-one	Compound 29 mp. 262 °C

Example B5

- Preparation of compound 5 2,4,8,15,18,26-hexaazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacosal(24),3,5,7(26),9,11,13(25),20,22-nonaene-6-carbonitrile, 14,17-dioxo-
- 10 Intermediate 13 (0.0009 mol) and DIPEA (0.0036 mol) were slowly added over 2 hours to a mixture of HBTU (0.00225 mol) in DMF (40 ml), then the reaction mixture was reacted for 1 hour at room temperature. After 3 hours, the reaction mixture was treated with water and the solvent was evaporated. The residue was purified by reversed-phase high-performance liquid chromatography. The pure fractions were collected and the
- 15 solvent was evaporated, yielding 0.017 g (14 %) of compound 5.

Example B6

Preparation of compound 6 21,17-metheno-15,11-nitrilo-1H,16H-pyrrolo[2,1-s][13,1,5,7,17,20]benzoxapentaazacyclotricosine-12-carbonitrile, 8-chloro-7-fluoro-2,3,5,10,23,24,25,26,27,27a-decahydro-20-methoxy-27-oxo-, (27aS)-

DIPEA (0.001884 mol) was added to a solution of intermediate 20 (0.000157 mol) in DMF dry (q.s.) and the mixture was stirred for 10 minutes, to give Solution (I).

Solution (I) was added dropwise to a solution of HBTU (0.000471 mol) in dry DMF

- 5 (40 ml) and the reaction mixture was stirred for 1 hour at room temperature. The solvent was evaporated and satd. aq. NaHCO₃ soln. with Na₂CO₃ (solid) was added to the residue. After extraction with DCM, the combined organic layers were dried (K₂CO₃), and the solvent was evaporated. The obtained residue was purified by reversed phase high-performance liquid chromatography (TFA-buffer). After
- 10 evaporation of the organic component of the eluent, NaHCO₃ was added and the product was isolated by extraction with DCM, yielding 0.011 g of compound 6.

Compounds that were prepared according to Example B6	
1H,7H-12,8-metheno-6,2-nitrilo-1,3,7,14,17-benzopentaazacycloeicosine-5-carbonitrile, 21-chloro-13,14,15,16,17,18-hexahydro-17-methyl-15-oxo-	Compound 30
21,17-metheno-15,11-nitrilo-16H-pyrrolo[2,1-r][13,1,5,7,16,19]benzoxapentaazacyclodocosine-12-carbonitrile, 8-chloro-7-fluoro-1,2,3,5,10,23,24,25,26,26a-decahydro-20-methoxy-26-oxo-, (26aS)-	Compound 31
12,8-metheno-6,2-nitrilo-7H-13,1,5,7,16,19-benzoxapentaazacyclodocosine-3-carbonitrile, 23-chloro-1,14,15,16,17,18,19,20-octahydro-11-methoxy-19-methyl-17-oxo-	Compound 32
1H,7H-12,8-metheno-6,2-nitrilo-13,1,5,7,17,20-benzoxapentaazacyclotricosine-3-carbonitrile, 24-chloro-14,15,16,17,18,19,20,21-octahydro-11-methoxy-20-methyl-18-oxo-	Compound 33 mp. 182.7-184.5 °C

Example B7

Preparation of compound 7 1H,7H-6,2:12,8-dimetheno-13,20,1,3,5,7-benzodioxatetraazacyclodocosine, 23-chloro-14,15,16,17,18,19-hexahydro-11-methoxy-

- 15 A solution of intermediate 24 (0.00014 mol), 1,1'-(azodicarbonyl)bis- piperidine (0.00021 mol) and tributyl- phosphine (0.00021 mol) in THF (10 ml) was stirred for 2

hours at room temperature and then the solvent was evaporated under reduced pressure. The obtained residue was purified by high-performance liquid chromatography. The product fractions were collected and the solvent was evaporated, yielding 0.009 g of compound 7.

5

Compounds that were prepared according to Example B7	
11H-6,10-metheno-5H-dibenzo[b,k][1,13,4,6,8,10]dioxatetraazacyclononadecine, 13-chloro-17,18,19,20,21,22-hexahydro-2-methoxy-	Compound 34 mp. 206 °C
1H,7H-2,6:12,8-dimetheno-14H-13,19,1,3,5,7-benzodioxatetraazacycloheneicosine, 22-bromo-15,16,17,18-tetrahydro-11-methoxy-	Compound 35
1H,7H-2,6:12,8-dimetheno-13,20,1,3,5,7-benzodioxatetraazacyclodocosine, 23-bromo-14,15,16,17,18,19-hexahydro-11-methoxy-	Compound 36
1H,7H-2,6:12,8-dimetheno-14H-13,21,1,3,5,7-benzodioxatetraazacyclotricosine, 24-bromo-15,16,17,18,19,20-hexahydro-11-methoxy-	Compound 37
1H,7H-2,6:12,8-dimetheno-13,22,1,3,5,7-benzodioxatetraazacyclotetracosine, 25-bromo-14,15,16,17,18,19,20,21-octahydro-11-methoxy-	Compound 38
1H,7H-2,6:12,8-dimetheno-14H-13,23,1,3,5,7-benzodioxatetraazacyclopentacosine, 26-chloro-15,16,17,18,19,20,21,22-octahydro-11-methoxy-	Compound 39
1H,7H-6,2:8,12-dimetheno-13,20,1,3,5,7-benzodioxatetraazacyclodocosine, 23-bromo-14,15,16,17,18,19-hexahydro-10-methoxy-	Compound 40

Example B8

Preparation of 2,4,6,8,15,22-hexaazatetracyclo[22.3.1.1~3,7~.1~9,13~]triaconta-
compound 8 1(28),3,5,7(30),9,11,13(29),24,26-nonaene-14,23-dione

To a solution of intermediate 29 (0.69 mmol) in DMF (100 ml), DIPEA (6.90 mmol) was added. This solution was added dropwise during 1 hour to a solution of
 10 (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (2.1 mmol) in DMF (100 ml) at room temperature. The reaction mixture was stirred further for 30 min at room temperature. The solvent was evaporated. The residue was dissolved in DCM, washed with 10% NaHCO₃ solution, then dried (MgSO₄), filtered and the solvent was

evaporated. The residue was suspended from acetonitrile, the precipitate was filtered off. The solid was recrystallized from acetonitrile, after cooling the solid was filtered off and dried in vacuum at 50°C, yielding 100 mg of compound 8, melting point 307°C.

Compound that was prepared according to Example B8	
2,4,6,8,15,21-hexaazatetracyclo[21.3.1.1~3,7~.1~9,13~]nonacosa-1(27),3,5,7(29),9,11,13(28),23,25-nonaene-14,22-dione	Compound 41 mp. 328 °C

5

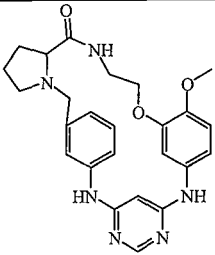
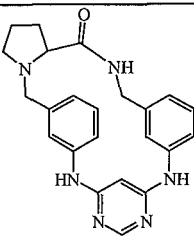
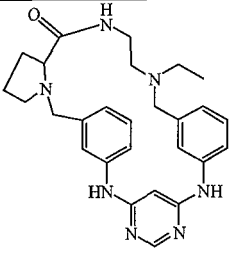
Example B9

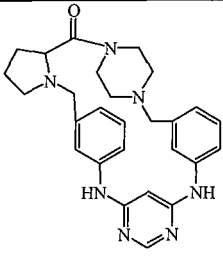
Preparation of 18-oxa-2,4,6,8,15-
compound 9 pentaazatetracyclo[17.2.2.1~3,7~.1~9,13~]pentacosa-3,5,7(25),9,11,13(24),19,21,22-nonaen-16-one, trifluoroacetic acid salt

A solution of intermediate 33 in DMF (20 ml) was added dropwise to a solution of HBTU (0.0003 mol) and DIPEA (0.0015 mol) in DMF (10 ml) while stirring. The reaction mixture was stirred for 30 minutes, the solvent was evaporated at 50°C under N₂. The obtained residue was purified by column chromatography [some residues were first purified with a NH₄OAc buffer and then with a TFA-buffer on a RP-column; other residues were purified directly with a TFA-buffer on a RP-column]. The product fractions were collected and then the solvent was evaporated and co-evaporated with CH₃CN/MeOH, yielding 0.034 g of compound 9, isolated as a trifluoroacetic acid salt (1:1).

15

Compounds that were prepared according to Example B9	
20-oxa-1,8,10,12,14,23-hexaazapentacyclo[21.2.2.1~3,7~.1~9,13~.1~15,19~]triaconta-3,5,7(30),9,11,13(29),15,17,19(28)-nonaen-22-one	Compound 42
1,8,10,12,14,23-hexaazapentacyclo[21.2.2.1~3,7~.1~9,13~.1~15,19~]triaconta-3,5,7(30),9,11,13(29),15,17,19(28)-nonaen-22-one	Compound 43
1,8,10,12,14,23-hexaazapentacyclo[21.2.2.2~15,18~.1~3,7~.1~9,13~]hentriaconta-3,5,7(31),9,11,13(30),15,17,28-nonaen-22-one, trifluoroacetic acid salt	Compound 44
1,8,10,12,14,22-hexaazapentacyclo[20.2.2.1~3,7~.1~9,13~.1~15,19~]nonacosa-3,5,7(29),9,11,13(28),15,17,19(27)-nonaen-21-one	Compound 45
14,20-dioxa-2,4,6,8,17-pentaazatetracyclo[19.2.2.1~3,7~.1~9,13~]heptacosa-	Compound 46

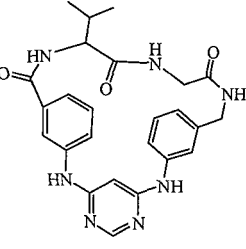
3,5,7(27),9,11,13(26),21,23,24-nonaen-18-one, 12-methoxy-, trifluoroacetic acid salt (1:1)	
2,4,6,8,15-pentaazatetracyclo[16.3.1.1~3,7~.1~9,13~]tetracos-1(22),3,5,7(24),9,11,13(23),18,20-nonaen-16-one, trifluoroacetic acid salt (1:1)	Compound 47
14-oxa-2,4,6,8,17-pentaazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacos-1(24),3,5,7(26),9,11,13(25),20,22-nonaen-18-one, 12-methoxy-, trifluoroacetic acid salt (1:1)	Compound 48
 $\cdot 2 \text{C}_2\text{HF}_3\text{O}_2$	Compound 49
2,4,6,8,15,18-hexaazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacos-1(24),3,5,7(26),9,11,13(25),20,22-nonaen-16-one, 18-methyl-, trifluoroacetic acid salt (1:1)	Compound 50
2,4,6,8,15,18,21-heptaazatetracyclo[21.3.1.1~3,7~.1~9,13~]nonacos-1(27),3,5,7(29),9,11,13(28),23,25-nonaen-17-one, 21-ethyl-15-methyl-, trifluoroacetic acid salt (1:3)	Compound 51
1,8,10,12,14,21,24-heptaazapentacyclo[22.2.2.1~3,7~.1~9,13~.1~15,19~]hentriaconta-3,5,7(31),9,11,13(30),15,17,19(29)-nonaen-23-one, 21-methyl-, trifluoroacetic acid salt (1:3)	Compound 52
 $2 \text{C}_2\text{HF}_3\text{O}_2$	Compound 53
 $3\text{C}_2\text{HF}_3\text{O}_2$	Compound 54
2,4,6,8,15,18-hexaazatetracyclo[19.3.1.1~3,7~.1~9,13~]heptacos-1(25),3,5,7(27),9,11,13(26),21,23-nonaen-19-one, 15-ethyl-, trifluoroacetic acid salt (1:3)	Compound 55

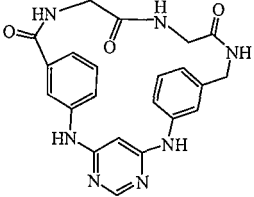
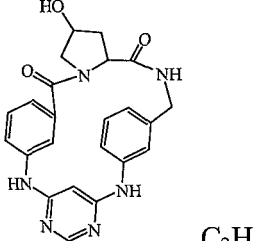
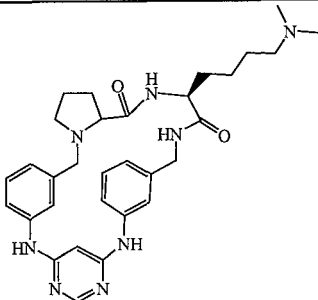
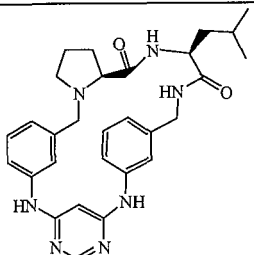
trifluoroacetic acid salt (1:2)	
 $\cdot 2 \text{ C}_2\text{HF}_3\text{O}_2$	Compound 56

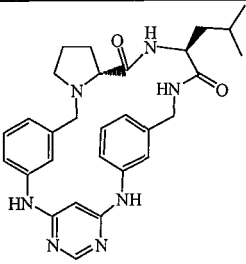
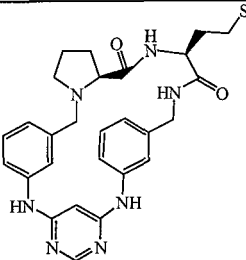
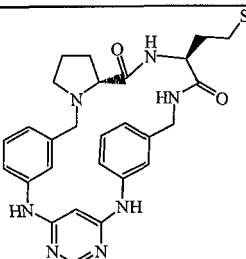
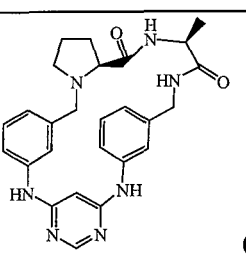
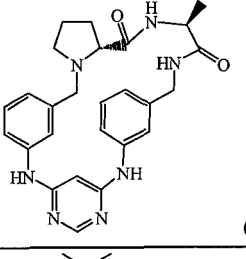
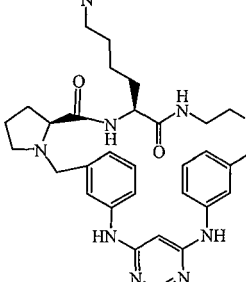
Example B10

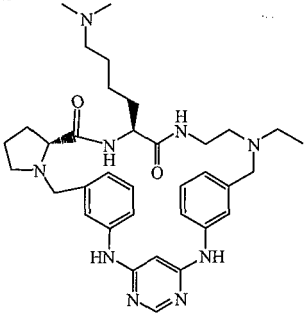
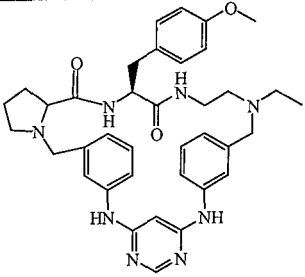
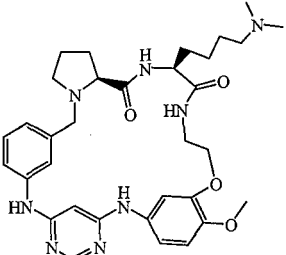
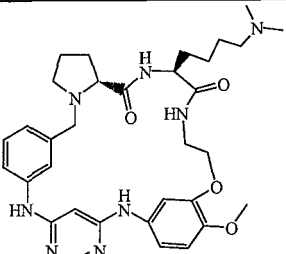
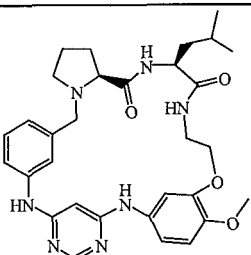
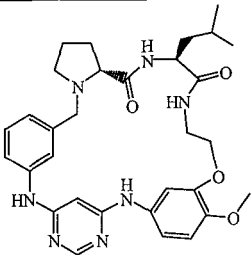
Preparation of compound 10 (RS)-2,4,6,8,15,18-hexaazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacosal(24),3,5,7(26),9,11,13(25),20,22-nonaene-14,17-dione, 16-(2-methylpropyl)- trifluoroacetic acid salt

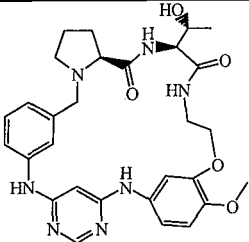
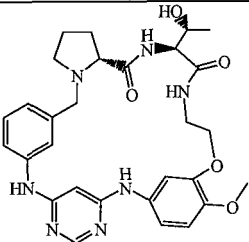
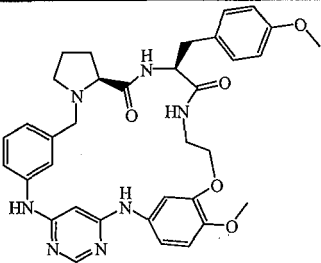
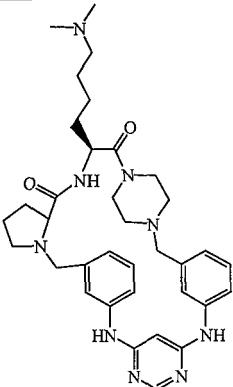
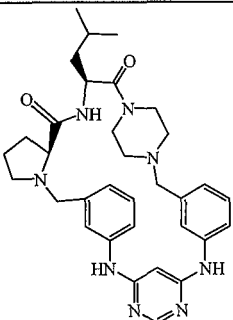
A solution of intermediate 37 in DMF (20 ml) was added dropwise to a solution of HBTU (0.0004 mol) and DIPEA (0.300 ml) in DMF (10 ml) while stirring. The reaction mixture was stirred for 30 minutes at room temperature, the solvent was evaporated at 50°C under N₂. The obtained residue was purified by column chromatography [some residues were first purified with a NH₄OAc buffer and then with a TFA-buffer on a RP-column; other residues were purified directly with a TFA-buffer on a RP-column]. The product fractions were collected and then the solvent was evaporated and co-evaporated with CH₃CN/MeOH, yielding 0.069 g of compound 10, isolated as a trifluoroacetic acid salt (1:1).

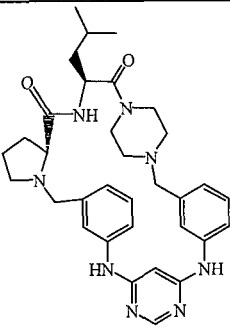
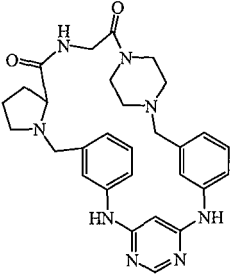
Compounds that were prepared according to Example B10	
2,4,6,8,15,23-hexaazatetracyclo[23.3.1.1~3,7~.1~9,13~]hentriacontal(29),3,5,7(31),9,11,13(30),25,27-nonaene-14,22-dione	Compound 57
2,4,6,8,15,21-hexaazatetracyclo[21.3.1.1~3,7~.1~9,13~]nonacosal(27),3,5,7(29),9,11,13(28),23,25-nonaene-14,20-dione	Compound 58
2,4,6,8,15,18-hexaazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacosal(24),3,5,7(26),9,11,13(25),20,22-nonaene-14,17-dione, 16-[4-(dimethylamino)butyl]-	Compound 59
 $\cdot \text{C}_2\text{HF}_3\text{O}_2$	Compound 60

 . C₂HF₃O₂	Compound 61
2,4,6,8,15,18-hexaazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacos-1(24),3,5,7(26),9,11,13(25),20,22-nonaene-14,17-dione, 16-[2-(methylthio)ethyl]-	Compound 62
2,4,6,8,15,18-hexaazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacos-1(24),3,5,7(26),9,11,13(25),20,22-nonaene-14,17-dione, 15-methyl-, trifluoroacetic acid salt (1:1)	Compound 63
2,4,6,8,15,18-hexaazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacos-1(24),3,5,7(26),9,11,13(25),20,22-nonaene-14,17-dione, 16-(1-hydroxyethyl)-, trifluoroacetic acid salt (1:1)	Compound 64
2,4,6,8,15,18-hexaazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacos-1(24),3,5,7(26),9,11,13(25),20,22-nonaene-14,17-dione, 16-(1H-imidazol-4-ylmethyl)-, trifluoroacetic acid salt (1:1)	Compound 65
 . C₂HF₃O₂	Compound 66
 . 2 C₂HF₃O₂ [(RS),(S)]	Compound 67
 C₂HF₃O₂ [(A),(S)]	Compound 68

 $C_2HF_3O_2 [(B),(S)]$	Compound 69
 $C_2HF_3O_2 [(A),(S)]$	Compound 70
 $C_2HF_3O_2 [(B),(S)]$	Compound 71
 $C_2HF_3O_2 [(A),(S)]$	Compound 72
 $C_2HF_3O_2 [(B),(S)]$	Compound 73
 $.3 C_2HF_3O_2 [(A),(S)]$	Compound 74

 .3 C₂HF₃O₂ [(B),(S)]	Compound 75
 . 2 C₂HF₃O₂ [(RS),(S)]	Compound 76
 . 2 C₂HF₃O₂ [(A),(S)]	Compound 77
 . 2 C₂HF₃O₂ [(B),(S)]	Compound 78
 C₂HF₃O₂ [(A),(S)]	Compound 79
 C₂HF₃O₂ [(B),(S)]	Compound 80

 $C_2HF_3O_2 [(A),(2S,3R)]$	Compound 81
 $C_2HF_3O_2 [(B),(2S,3R)]$	Compound 82
 $C_2HF_3O_2 [(A),(S)]$	Compound 83
 $. 3 C_2HF_3O_2 [(RS),(S)]$	Compound 84
 $. 2 C_2HF_3O_2 [(A),(S)]$	Compound 85

 . 2 C₂HF₃O₂ [(B),(S)]	Compound 86
 . 2 C₂HF₃O₂ [(RS)]	Compound 87

Example B11

Preparation of compound 11

14-oxa-2,4,6,8,17,20-hexaazatetracyclo[20.3.1.1~3,7~.1~9,13~]octacosal(26),3,5,7(28),9,11,13(27),22,24-nonaen-18-one, 12-methoxy-20-methyl-

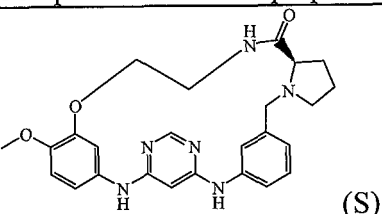
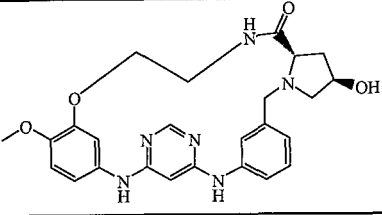
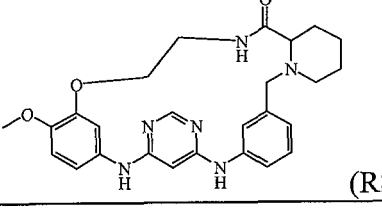
DIPEA (0.012 mol) was added to a solution of intermediate 44(0.002 mol) in 50 mL of dry DMF (q.s.) and then this solution was added dropwise to a mixture of HBTU (0.006 mol) in 150 mL of dry DMF (q.s.). The resulting mixture was stirred for 30 minutes at room temperature and the solvent was evaporated. PS-NMe₃(+)-HCO₃(-) (Novabiochem, cat. 01-64-0419) was added and the mixture was shaken overnight. After filtration, Silica-SO₃H (Acros, cat. 360220050) (0.016 mol) was added portionwise to "catch" the product, then the reaction mixture was filtered over a plug of silica gel and washed with DCM/MeOH (9:1). The product was then released by washing with DCM/7 N NH₃ in MeOH (9:1) and, upon evaporation of the solvent, triturated with MeOH. Filtration of the precipitate provided 0.1024g of the pure product. The mother liquor and washings of the silica gel were combined and purified by reversed phase HPLC (NH₄OAc buffer) yielding a second batch of product, yielding 0.0581 g of compound 11.

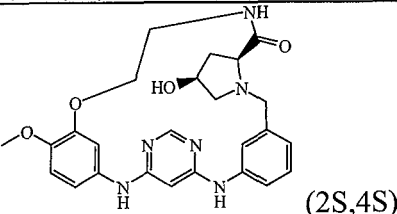
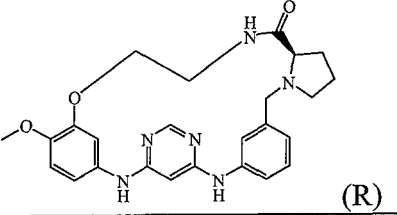
The compound could be isolated in two ways:

1. Catch and release: The solvent was concentrated to about 100 mL after which PS-NMe₃(+)-HCO₃(-) (Novabiochem, cat. 01-64-0419) (0.012 mol) was added. The

resulting suspension was shaken overnight to scavenge 1-hydroxybenzotriazole (HOBt). After filtration and washing with DMF, Silica-SO₃H (Acros, cat. 360220050) (0.016 mol) was added portionwise to catch the compound, then the reaction mixture was filtered over silica gel and washed with DCM/MeOH (90/10). The desired product was then released by washing with 10% 7 N NH₃/MeOH in DCM. After evaporation of the solvent, MeOH was added, and the resulting precipitate was filtered off giving pure compound 11 (0.1024 g, 12 % from intermediate 63).

Reversed Phase HPLC: Alternatively, the reaction mixture after macrocyclization can be evaporated to dryness and directly purified by high-performance liquid chromatography (NH₄OAc buffer). In this case compound 11 can be obtained in 20% yield from intermediate 63, mp. 286.3-288.1 °C.

Compounds that were prepared according to Example B11	
 (S)	Compound 88 mp. 279.0-281.2 °C
 (2S-trans)	Compound 89 mp. 287.8-289.1 °C
 (RS)	Compound 90 mp. 292.9-295.5 °C
20-oxa-1,8,10,12,14,23-hexaazapentacyclo[23.3.1.1~3,7~.1~9,13~.1~15,19~]dotriaconta-3,5,7(32),9,11,13(31),15,17,19(30)-nonaen-24-one, 18-methoxy- (RS)	Compound 91 mp. 281.0-285.6 °C
20-oxa-1,8,10,12,14,23-hexaazapentacyclo[23.2.2.1~3,7~.1~9,13~.1~15,19~]dotriaconta-3,5,7(32),9,11,13(31),15,17,19(30)-nonaen-24-one, 18-methoxy-	Compound 92 mp. 297.9-298.2 °C
20-oxa-1,8,10,12,14,23-hexaazapentacyclo[24.2.2.1~3,7~.1~9,13~.1~15,19~]tritriaconta-3,5,7(33),9,11,13(32),15,17,19(31)-nonaen-24-one, 18-methoxy-	Compound 93 mp. 296.9-299.5 °C

20-oxa-1,8,10,12,14,23,26-heptaazapentacyclo[24.2.2.1~3,7~.1~9,13~.1~15,19~]tritriaconta-3,5,7(33),9,11,13(32),15,17,19(31)-nonaen-24-one, 18-methoxy-	Compound 94 mp. 267.7-269.0 °C
 (2S,4S)	Compound 95
 (R)	Compound 96
20-oxa-1,8,10,12,14,23,27-heptaazapentacyclo[26.2.2.1~3,7~.1~9,13~.1~15,19~]pentatriaconta-3,5,7(35),9,11,13(34),15,17,19(33)-nonaen-24-one, 18-methoxy-	Compound 97
14-oxa-2,4,6,8,17,21-hexaazatetracyclo[21.3.1.1~3,7~.1~9,13~]nonacosa-1(27),3,5,7(29),9,11,13(28),23,25-nonaen-18-one, 12-methoxy-21-(phenylmethyl)-	Compound 98
20-oxa-1,8,10,12,14,23-hexaazapentacyclo[23.3.1.1~3,7~.1~9,13~.1~15,19~]dotriaconta-3,5,7(32),9,11,13(31),15,17,19(30)-nonaen-24-one, 26-hydroxy-18-methoxy-	Compound 99
14-oxa-2,4,6,8,17,20-hexaazatetracyclo[20.3.1.1~3,7~.1~9,13~]octacosa-1(26),3,5,7(28),9,11,13(27),22,24-nonaen-18-one, 20-ethyl-12-methoxy-	Compound 100
14-oxa-2,4,6,8,17,22-hexaazatetracyclo[22.3.1.1~3,7~.1~9,13~]triaconta-1(28),3,5,7(30),9,11,13(29),24,26-nonaen-18-one, 12-methoxy-22-methyl-	Compound 101
14-oxa-2,4,6,8,17,21-hexaazatetracyclo[21.3.1.1~3,7~.1~9,13~]nonacosa-1(27),3,5,7(29),9,11,13(28),23,25-nonaen-18-one, 12-methoxy-21-phenyl-	Compound 102

Example B12

Preparation of compound 12 6,2:12,8-dimetheno-7H-13,1,3,5,7,17,20-benzoxahexaazacyclotetracosine-18,21-dione, 25-chloro-1,14,15,16,17,19,20,22-octahydro-11-methoxy-19-(2-methylpropyl)-, (19S)-

A mixture of intermediate 49 (0.0062 mol), HBTU (0.0081 mol) and triethylamine (0.0187 mol) in DCM/THF/DMF (170ml) was stirred at room temperature for 4 hours, poured out into water and extracted with EtOAc. The organic layer was washed with saturated NaHCO₃, dried (MgSO₄), filtered, and the solvent was evaporated till dryness. The residue was crystallized from DCM/MeOH. The precipitate was filtered off, washed with DCM, diethyl ether then dried in vacuo. The solid was recrystallized in THF. Addition of DIPE to the filtrate gave a second batch of compound 12 (L)-(S), melting point 191°C.

10

Compounds that were prepared according to Example B12	
1H,7H-6,2:12,8-dimetheno-13,1,3,5,7,16,19-benzoxahexaazacyclotricosine-17,20(14H)-dione, 24-chloro-15,16,18,19,21-pentahydro-11-methoxy-	Compound 103 mp. 240 °C
6,2:12,8-dimetheno-7H-13,1,3,5,7,17,20-benzoxahexaazacyclotetracosine-18,21-dione, 1,14,15,16,17,19,20,22-octahydro-11-methoxy-17-[2-(4-morpholinyl)ethyl]-, trifluoroacetic acid salt	Compound 104 mp. 154 °C
6,2:8,12-dimetheno-7H-13,1,3,5,7,17,20-benzoxahexaazacyclotetracosine-18,21-dione, 25-chloro-1,14,15,16,17,19,20,22-octahydro-11-methoxy-19,19-dimethyl-	Compound 105 mp. >250 °C
1H,7H-6,2:8,12-dimetheno-13,1,3,5,7,16,19-benzoxahexaazacyclotricosine-17,20(14H)-dione, 24-chloro-15,16,18,19,21-pentahydro-18,18-dimethyl-11-[3-(4-morpholinyl)propoxy]-	Compound 106 mp. >260 °C
1H,7H-6,2:8,12-dimetheno-13,1,3,5,7,16,19-benzoxahexaazacyclotricosine-17,20(14H)-dione, 24-chloro-15,16,18,19,21-pentahydro-11-[3-(4-morpholinyl)propoxy]-, hydrochloric acid salt (1:2)	Compound 107 mp. 180 °C

Example B13

Preparation of 1H,7H-6,2:8,12-dimetheno-13,20,1,3,5,7,17-

compound 13 benzodioxapentaazacyclodocosine, 23-chloro-14,15,16,17,18,19-hexahydro-11-methoxy-

Intermediate 56 (0.0083 mol) was dissolved in DCM/MeOH. Toluene was added. The mixture was evaporated in vacuo. The residue was suspended in THF (160ml).

Triphenylphosphine (0.0248 mol) was added. A solution of DIAD (0.0247 mol) in THF (50ml) was added dropwise. The mixture was stirred at room temperature overnight

- 5 then evaporated in vacuo. The residue was partitioned between water and EtOAc/diethyl ether. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated in vacuo. The residue was purified by column chromatography over silica gel (eluent: DCM/MeOH/NH₄OH 96/4/0.3; 20-45μm), yielding 1.44 g of a off white solid. It was then triturated with acetonitrile/isopropyl ether, filtered off and
- 10 dried in vacuo, yielding 0.995g of compound 13, mp. >260 °C .

Compound that was prepared according to Example B13	
14,20-dioxa-2,4,6,8,17-pentaazatetracyclo[19.3.1.1~3,7~.1~9,13~]heptacos-1(25),3,5,7(27),9,11,13(26),21,23-nonaen-16-one, 12,22-dimethoxy-	Compound 108 mp. 257 °C

Example B14

Preparation of 2,4,6,8,15,18-hexaazatetracyclo[18.3.1.1~3,7~.1~9,13~]hexacos-
compound 14 1(24),3,5,7(26),9,11,13(25),20,22-nonaen-14-one, 23-methoxy-

A mixture of intermediate 62 (0.00021 mol), HBTU (0.00053 mol) and DIPEA
15 (0.00084 mol) in DMF (100 ml) and piperidine (10 ml) was reacted for 3 hours at room temperature, then morpholine (10 ml) was added and after 90 minutes the solvent was evaporated. The residue was purified by reversed-phase high-performance liquid chromatography. The desired product fractions were collected and the solvent was evaporated, yielding 0.008 g of compound 14.

20

Compound that was prepared according to Example B14	
14-oxa-2,4,6,8,17-pentaazatetracyclo[17.3.1.1~3,7~.1~9,13~]pentacos-1(23),3,5,7(25),9,11,13(24),19,21-nonaen-18-one, 12-methoxy-	Compound 109

Example B15

Preparation of 14-oxa-2,4,6,8,17,20-
compound 15 hexaazatetracyclo[20.3.1.1~3,7~.1~9,13~]octacos-1(26),3,5,7(28),9,11,13(27),22,24-nonaen-18-one, 12-methoxy-19-

(phenylmethyl)-

- DIPEA (0.0050 mol) was added to a solution of intermediate 64 (0.0005 mol) in DMF dry (30 ml) and the mixture was stirred, then the obtained solution was added dropwise to a solution of HBTU (0.0015 mol) in DMF dry (100 ml) and after 1 hour the solvent was evaporated. DCM, water and potassium carbonate were added and the reaction mixture was shaken. The organic layer was separated and the aqueous layer was extracted 2 times with DCM. The organic layers were combined, dried (anhydrous potassium carbonate), filtered off and the solvent was evaporated to dryness. The obtained residue was purified by reversed-phase high-performance liquid chromatography (NH₄OAc). The product fractions were collected and the solvent was evaporated. The residue (0.0491 g - 19 %) was dissolved in MeOH/DCM (10/90), then the resulting mixture was filtered through Extrelut and the solvent was evaporated, yielding 0.0353 g (14 %) of compound 15.

Example B16

Preparation of 6,2:12,8-dimetheno-7H-13,1,3,5,7,19-
compound 16 benzoxapentaazacyclodocosine, 23-chloro-22-fluoro-
 1,14,15,16,17,18,19,20-octahydro-11-(2-methoxyethoxy)-19-methyl-

- A solution of 1,1'-(azodicarbonyl)bis- piperidine (0.0013 mol) in THF (3ml) and a solution of tributyl- phosphine (0.0013 mol) in THF (3ml) were added dropwise simultaneously to a solution of intermediate 70 (0.0008 mol) in THF/DMF 80/20 (22ml) over a period of 30 minutes. The mixture was stirred at room temperature over the week-end, then poured out into potassium carbonate 10% and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated till dryness. The crude oil (1.9g) was crystallized from acetonitrile. The precipitate was filtered off and dried. The residue (0.46g) was purified by column chromatography over silica gel (eluent: DCM 100 then DCM/MeOH 98/2; 15-40μm). The pure fractions were collected and the solvent was evaporated. The residue (0.23g, 52%) was crystallized from acetonitrile. The precipitate was filtered off and dried, yielding 0.197g (44%) of compound 16, melting point 203°C.

Example B17

Preparation of 3,5,7,14,17-
compound 17 pentaazapentacyclo[19.2.2.2~14,17~.1~2,6~.1~8,12~]nonacosa-
 2,4,6(29),8,10,12(28),21,23,24-nonaen-18-one, trifluoroacetic acid salt

A solution of intermediate 73 in DMF (20 ml) was added dropwise to a solution of HBTU (0.0004 mol) and DIPEA (0.300 ml) in DMF (10 ml) while stirring. The reaction mixture was stirred for 30 minutes, the solvent was evaporated at 50°C under N₂. The obtained residue was purified by column chromatography [some residues were first purified with a NH₄OAc buffer and then with a TFA-buffer on a RP-column; other residues were purified directly with a TFA-buffer on a RP-column]. The product fractions were collected and then the solvent was evaporated and co-evaporated with acetonitrile/MeOH, yielding 0.014 g of compound 17, isolated as a trifluoroacetic acid salt (1:1).

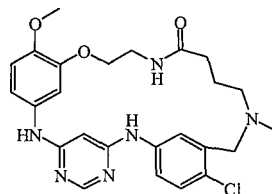
Compound that was prepared according to Example B17

1,8,10,12,22-pentaazapentacyclo[20.2.2.1~3,7~.1~9,13~.1~14,18~]nonacos-3,5,7(29),9,11,13(28),14,16,18(27)-nonaen-21-one, trifluoroacetic acid salt (1:1)

Compound 110

Example B18

Preparation of compound 111

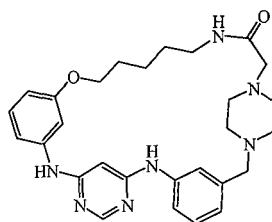


.C₂HF₃O₂ (1:1)

DIPEA (0.000750 mol) was added to mixture intermediate 79 (0.000250 mol) in 10 ml of DMF. This mixture was added dropwise to a solution of HBTU (0.000750 mol) in DMF (20 ml) over a 2-hour period. The reaction mixture was stirred for 30 minutes. The solvent was evaporated (oil-pump vacuum). The residue was purified by HPLC. The product fractions were collected and the solvent was evaporated, yielding compound 111.

Example B19

Preparation of compound 112

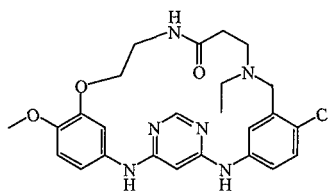


.C₂HF₃O₂ (1:1)

A solution of intermediate 85 (crude) in DMF (20 ml) was added dropwise to a solution of HBTU (0.00040 mol) and DIPEA (0.300 ml) in DMF (10 ml) and after stirring for 10 minutes at room temperature, the solvent was evaporated. The obtained residue was purified by reversed-phase high-performance liquid column chromatography [first
5 purified with a NH_4OAc buffer and then desalted with a TFA-buffer on a RP-column]. The product fractions were collected and then the solvent was evaporated (GeneVac), yielding 0.061 g of compound 112.

Example B20

Preparation of compound 113

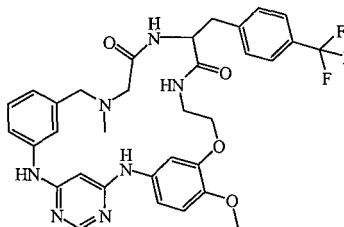


10 DIPEA (0.015 mol) was added to a solution of intermediate 95 (0.0025 mol) in DMF dry (10 mL) and this solution was added dropwise to a mixture of HBTU (0.0075 mol) in DMF dry (20 mL). The resulting mixture was stirred for 30 minutes at room temperature and the solvent was evaporated. The residue was purified by reversed phase HPLC (NH_4OAc buffer), yielding 0.014 g of compound 113.

15

Example B21

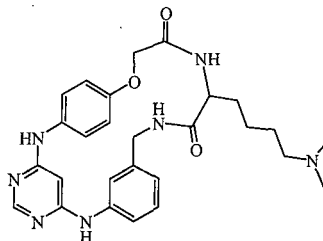
Preparation of compound 114



. $\text{C}_2\text{HF}_3\text{O}_2$ (1:1)

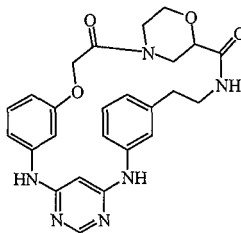
A solution of intermediate 93 (crude) in DMF (20 ml) was added dropwise to a solution of HBTU (0.00040 mol) and DIPEA (0.300 ml) in DMF (10 ml) and after stirring for 10 minutes at room temperature, the solvent was evaporated. The obtained residue was
20 purified by reversed-phase high-performance liquid column chromatography using an eluent with an NH_4OAc buffer on prelines. The product fractions were collected and then the solvent was evaporated. The residues were desalted then by reversed-phase HPLC using a TFA buffer. The product fractions were collected and the solvent was evaporated (Genevac), yielding 0.008 g of compound 114.

25

Example B22Preparation of compound 115

.C₂HF₃O₂ (1:1)

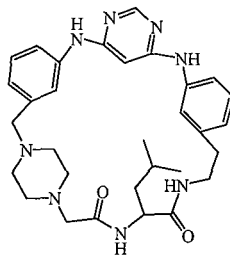
A solution of intermediate 107 (crude) in DMF (20 ml) was added dropwise to a solution of HBTU (0.00040 mol) and DIPEA (0.300 ml) in DMF (10 ml) and after stirring for 30 minutes at room temperature, the solvent was evaporated under a N₂ flow at 70°C. The obtained residue was purified by reversed-phase high-performance liquid column chromatography using an eluent with an NH₄OAc buffer on prelines. The product fractions were collected and then the solvent was evaporated. The residues were desalted then by reversed-phase HPLC on prelines using a TFA buffer. The product fractions were collected and the solvent was evaporated (Genevac), yielding 0.007 g of compound 115.

Example B23Preparation of compound 116

.C₂HF₃O₂ (1:1)

(RS)

A solution of intermediate 108 (crude) in DMF (20 ml) was added dropwise (using a multichannel pump) to a solution of HBTU (0.00040 mol) and DIPEA (0.300 ml) in D (10 ml) and after stirring for 10 minutes at room temperature, the solvent was evaporated. The obtained residue was purified by reversed-phase high-performance liquid column chromatography [first purified with a NH₄OAc buffer (by prelines) and then desalted with a TFA-buffer on a RP-column (by prelines)]. The product fractions were collected and then the solvent was evaporated, yielding 0.009 g of compound 116.

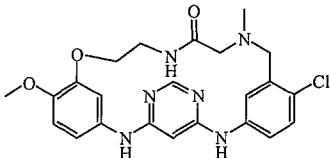
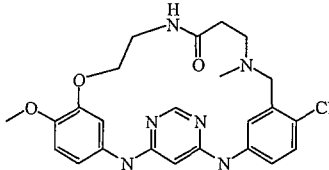
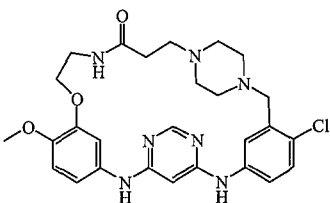
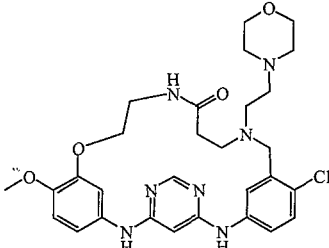
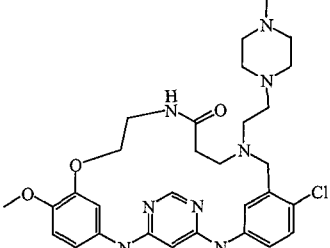
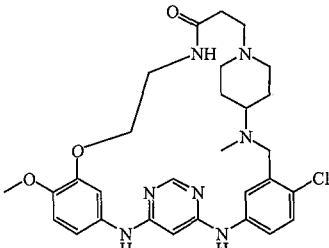
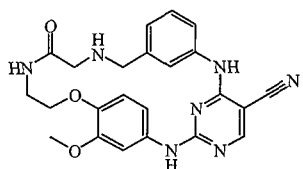
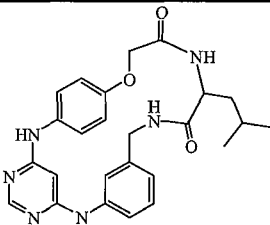
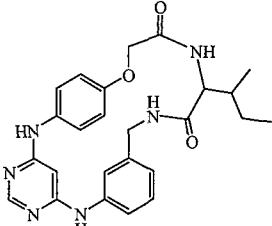
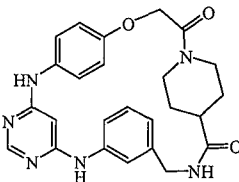
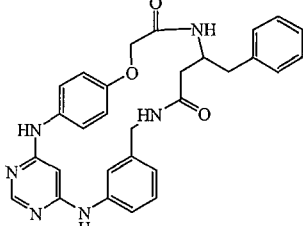
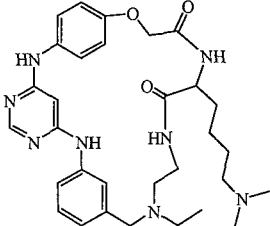
Example B24Preparation of compound 117
 $\text{C}_2\text{HF}_3\text{O}_2$ (1:1)

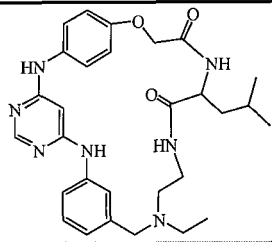
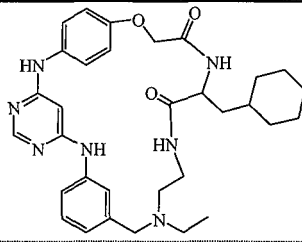
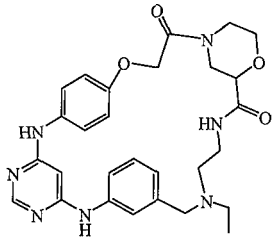
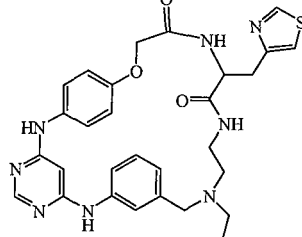
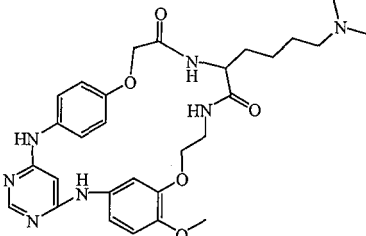
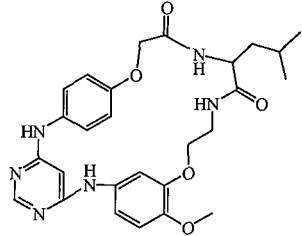
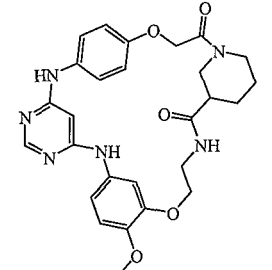
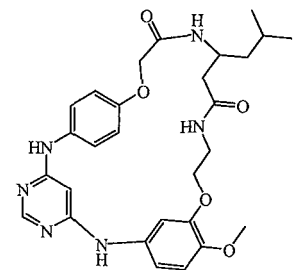
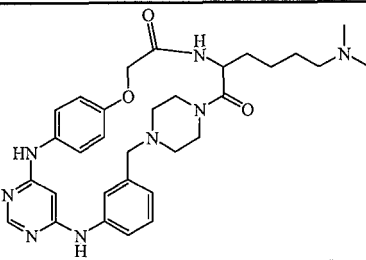
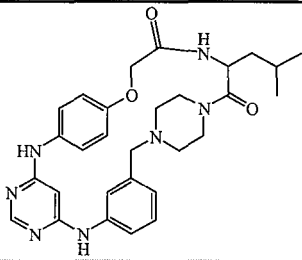
A solution of intermediate 109 (crude) in DMF (20 ml) was added dropwise (using a Watson-Marlow multichannel pump) to a solution of HBTU (0.00040 mol) and DIPEA (0.300 ml) in DMF (10 ml) and after stirring for 10 minutes at room temperature, the solvent was evaporated. The obtained residue was purified by reversed-phase high-performance liquid column chromatography [first purified with a NH_4OAc buffer (by prelines) and then desalted with a TFA-buffer on a RP-column (by prelines)]. The product fractions were collected and then the solvent was evaporated, yielding 0.023 g of compound 117.

Table F-1 lists the compounds that were prepared according to one of the above Examples. The following abbreviations were used in the tables : $\text{C}_2\text{HF}_3\text{O}_2$ stands for the trifluoroacetate salt.

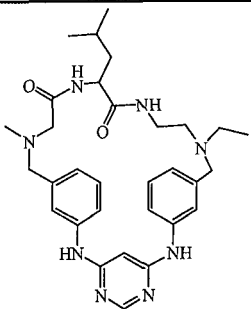
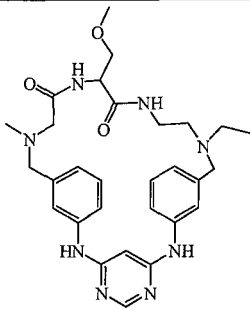
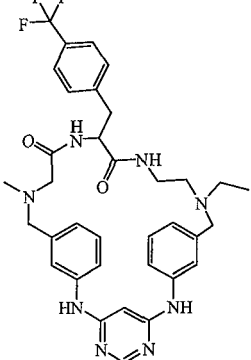
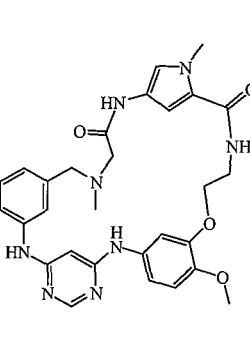
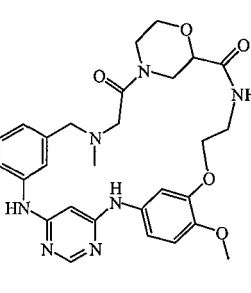
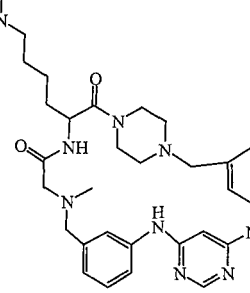
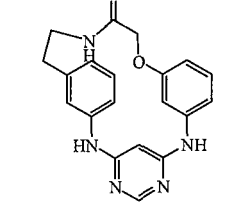
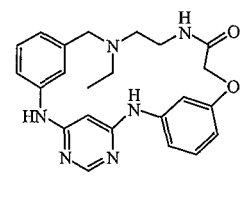
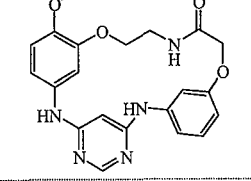
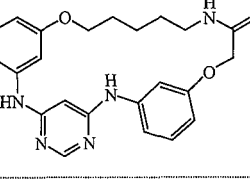
Table F-1

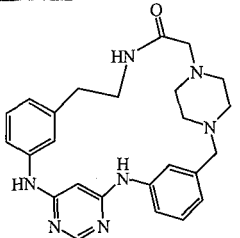
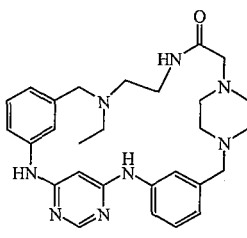
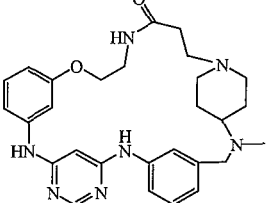
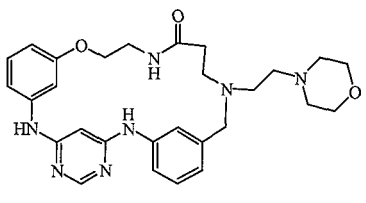
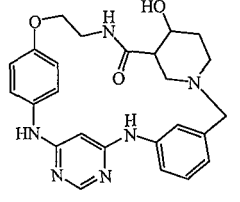
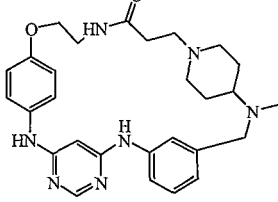
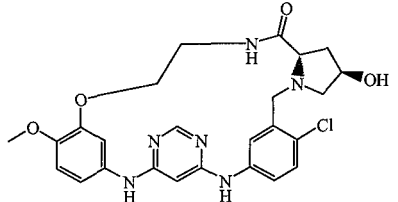
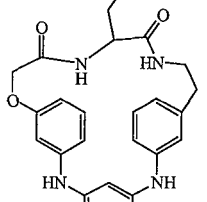
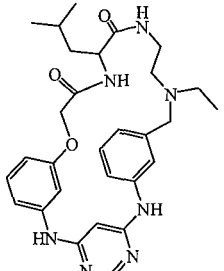
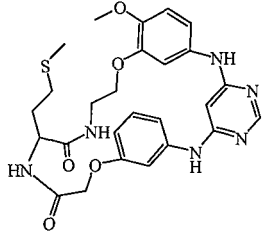
.2 $\text{C}_2\text{HF}_3\text{O}_2$; Co. No.118; Ex. [B20]	Co. No. 119; Ex. [B20]
Co. No. 120; Ex. [B20]	Co. No. 121; Ex. [B20]

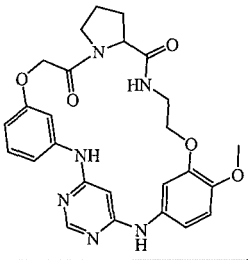
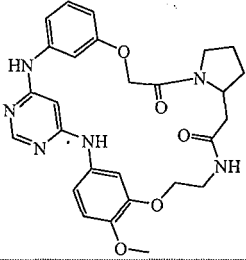
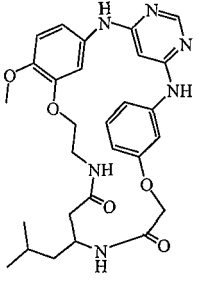
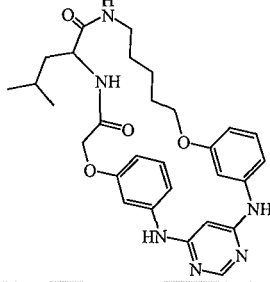
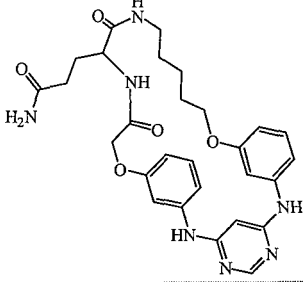
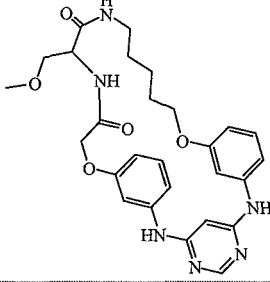
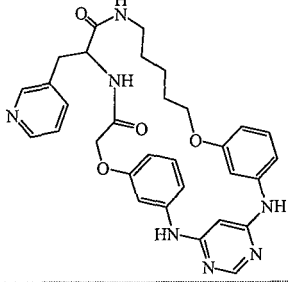
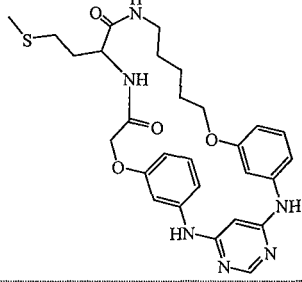
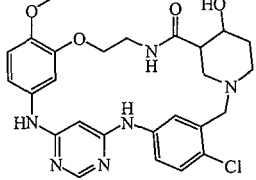
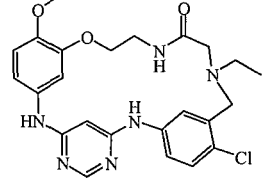
	
Co. No. 122; Ex. [B20]	Co. No. 123; Ex. [B20]
	
Co. No. 124; Ex. [B19]	Co. No. 125; Ex. [B20]
	
Co. No. 126; Ex. [B20]	Co. No. 127; Ex. [B20]
	
Co. No. 128; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 129; Ex. [B22]
	
.C ₂ HF ₃ O ₂ ; Co. No. 130; Ex. [B22]	.C ₂ HF ₃ O ₂ ; Co. No. 131; Ex. [B23]
	
.C ₂ HF ₃ O ₂ ; Co. No. 132; Ex. [B22]	.C ₂ HF ₃ O ₂ ; Co. No. 133; Ex. [B22]

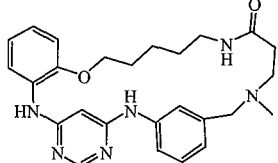
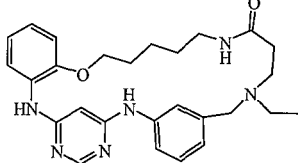
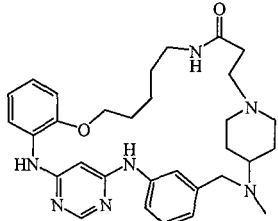
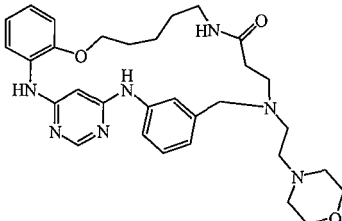
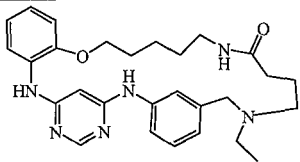
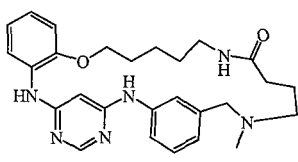
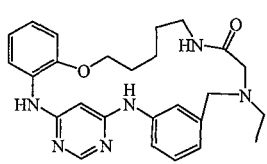
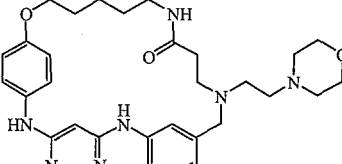
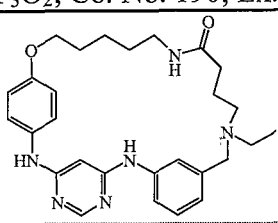
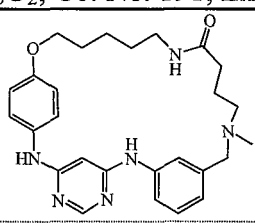
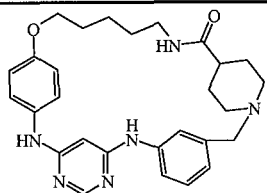
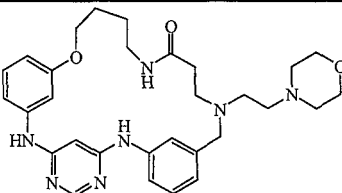
	
.C ₂ HF ₃ O ₂ ; Co. No. 134; Ex. [B22]	.C ₂ HF ₃ O ₂ ; Co. No. 135; Ex. [B22]
	
.C ₂ HF ₃ O ₂ ; Co. No. 136; Ex. [B22]	.C ₂ HF ₃ O ₂ ; Co. No. 137; Ex. [B22]
	
.C ₂ HF ₃ O ₂ ; Co. No. 138; Ex. [B21]	.C ₂ HF ₃ O ₂ ; Co. No. 139; Ex. [B21]
	
.C ₂ HF ₃ O ₂ ; Co. No. 140; Ex. [B22]	.C ₂ HF ₃ O ₂ ; Co. No. 141; Ex. [B21]
	
.C ₂ HF ₃ O ₂ ; Co. No. 142; Ex. [B21]	.C ₂ HF ₃ O ₂ ; Co. No. 143; Ex. [B21]

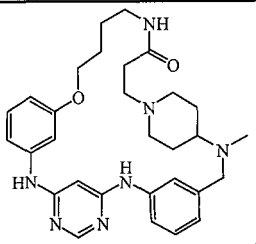
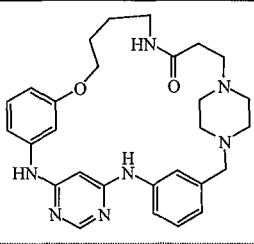
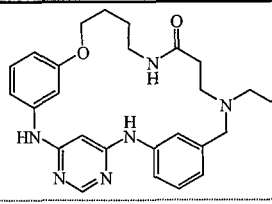
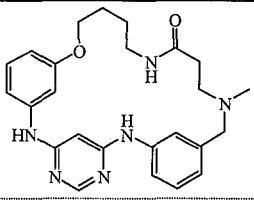
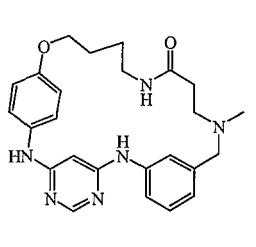
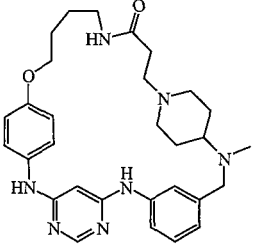
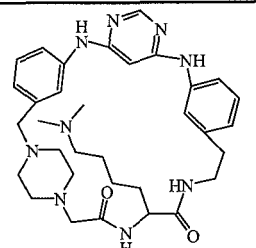
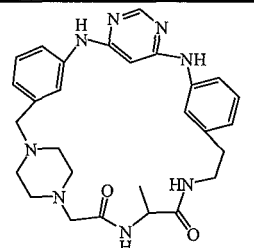
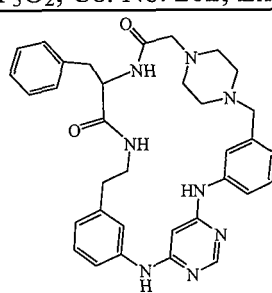
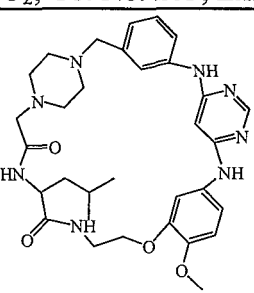
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Co. No. 146; Ex. [B20]	Co. No. 147; Ex. [B19]
.C ₂ HF ₃ O ₂ ; Co. No. 148; Ex. [B22]	.C ₂ HF ₃ O ₂ ; Co. No. 149; Ex. [B22]
.C ₂ HF ₃ O ₂ ; Co. No. 150; Ex. [B22]	.C ₂ HF ₃ O ₂ ; Co. No. 151; Ex. [B22]
.C ₂ HF ₃ O ₂ ; Co. No. 152; Ex. [B22]	Co. No. 153; Ex. [B21]

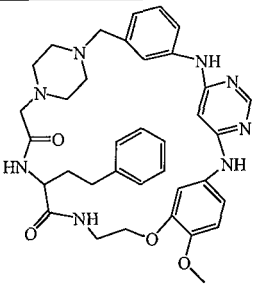
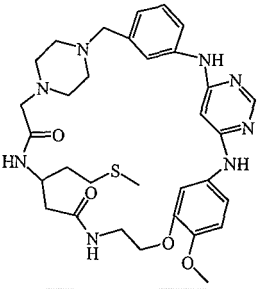
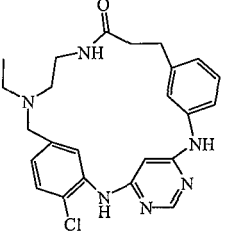
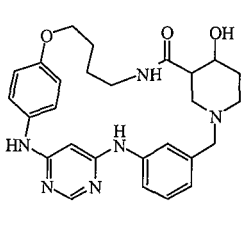
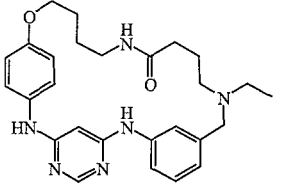
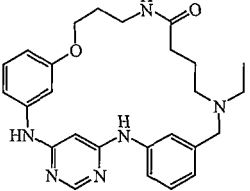
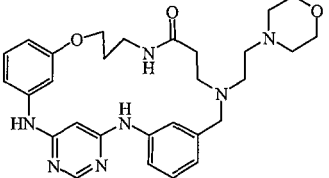
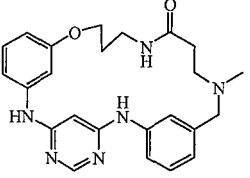
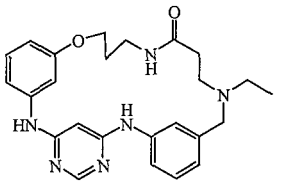
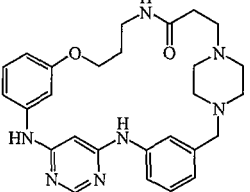
	
.C ₂ HF ₃ O ₂ ; Co. No. 154; Ex. [B21]	.C ₂ HF ₃ O ₂ ; Co. No. 155; Ex. [B21]
	
.C ₂ HF ₃ O ₂ ; Co. No. 156; Ex. [B21]	.C ₂ HF ₃ O ₂ ; Co. No. 157; Ex. [B22]
	
.C ₂ HF ₃ O ₂ ; Co. No. 158; Ex. [B22]; (RS)	.C ₂ HF ₃ O ₂ ; Co. No. 159; Ex. [B21]
	
.C ₂ HF ₃ O ₂ ; Co. No. 160; Ex. [B19]	.C ₂ HF ₃ O ₂ ; Co. No. 161; Ex. [B19]
	
.C ₂ HF ₃ O ₂ ; Co. No.162; Ex. [B19]	.C ₂ HF ₃ O ₂ ; Co. No. 163; Ex. [B19]

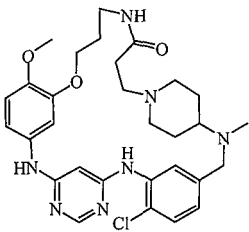
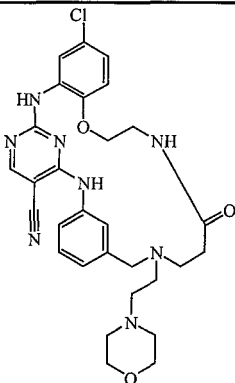
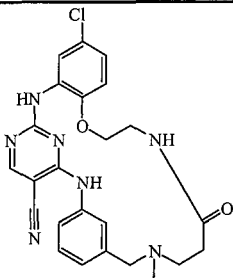
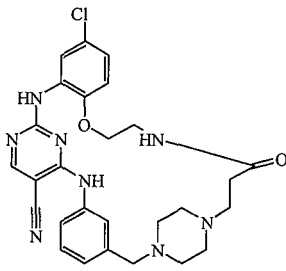
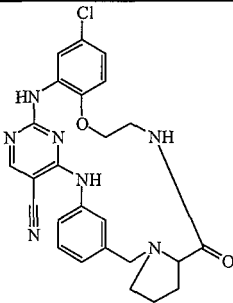
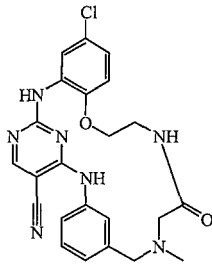
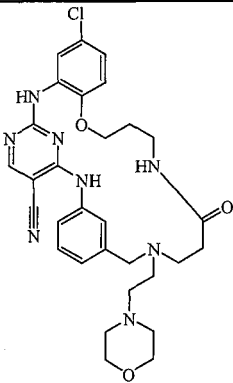
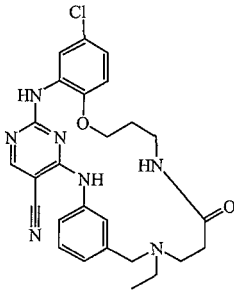
	
.C ₂ HF ₃ O ₂ ; Co. No. 164; Ex. [B19]	.C ₂ HF ₃ O ₂ ; Co. No. 165; Ex. [B19]
	
.C ₂ HF ₃ O ₂ ; Co. No. 166; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 167; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 168; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 169; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 170; Ex. [B20]; (2S-TRANS)	.C ₂ HF ₃ O ₂ ; Co. No. 171; Ex. [B22]
	
.C ₂ HF ₃ O ₂ ; Co. No. 172; Ex. [B22]	.C ₂ HF ₃ O ₂ ; Co. No. 173; Ex. [B21]

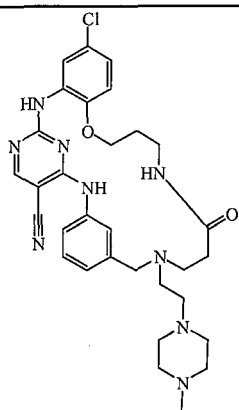
	
.C ₂ HF ₃ O ₂ ; Co. No. 174; Ex. [B22]	.C ₂ HF ₃ O ₂ ; Co. No. 175; Ex. [B22]
	
.C ₂ HF ₃ O ₂ ; Co. No. 176; Ex. [B21]	.C ₂ HF ₃ O ₂ ; Co. No. 177; Ex. [B21]
	
.C ₂ HF ₃ O ₂ ; Co. No. 178; Ex. [B21]	.C ₂ HF ₃ O ₂ ; Co. No. 179; Ex. [B21]
	
.C ₂ HF ₃ O ₂ ; Co. No. 180; Ex. [B21]	.C ₂ HF ₃ O ₂ ; Co. No. 181; Ex. [B21]
	
.C ₂ HF ₃ O ₂ ; Co. No. 182; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 183; Ex. [B20]

	
.C ₂ HF ₃ O ₂ ; Co. No. 184; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 185; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 186; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 187; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 188; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 189; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 190; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 191; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 192; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 193; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 194; Ex. [B20]	Co. No. 195; Ex. [B20]

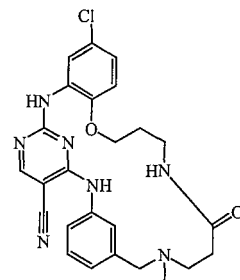
	
Co. No. 196; Ex. [B20]	Co. No. 197; Ex. [B19]
	
Co. No. 198; Ex. [B20]	Co. No. 199; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No.200; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 201; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 202; Ex. [B24]	.C ₂ HF ₃ O ₂ ; Co. No. 203; Ex. [B24]
	
.C ₂ HF ₃ O ₂ ; Co. No. 204; Ex. [B24]	.C ₂ HF ₃ O ₂ ; Co. No. 205; Ex. [B24]

	
.C ₂ HF ₃ O ₂ ; Co. No. 206; Ex. [B24]	.C ₂ HF ₃ O ₂ ; Co. No. 207; Ex. [B24]
	
.C ₂ HF ₃ O ₂ ; Co. No. 208; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 209; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 210; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 211; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 212; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 213; Ex. [B20]
	
.C ₂ HF ₃ O ₂ ; Co. No. 214; Ex. [B20]	.C ₂ HF ₃ O ₂ ; Co. No. 215; Ex. [B19]

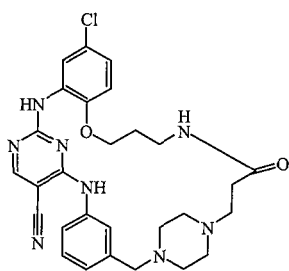
	
.C ₂ HF ₃ O ₂ ; Co. No. 216; Ex. [B20]	Co. No. 217; Ex. [B20]
	
Co. No. 218; Ex. [B20]	Co. No. 219; Ex. [B19]
	
Co. No. 220; Ex. [B20]	Co. No. 221; Ex. [B20]
	
Co. No. 222; Ex. [B20]	Co. No. 223; Ex. [B20]



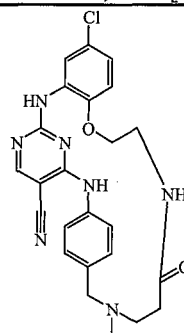
Co. No. 224; Ex. [B20]



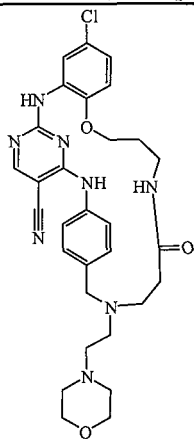
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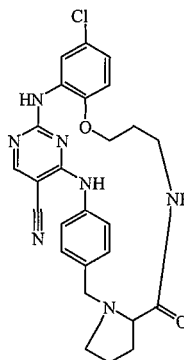
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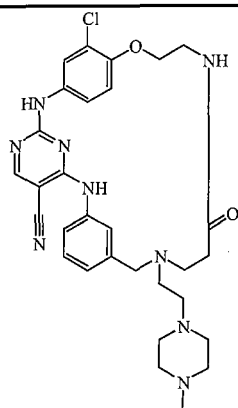
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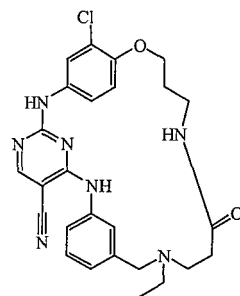
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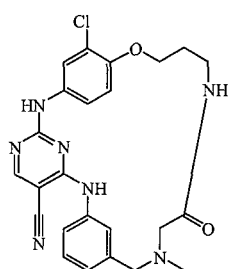
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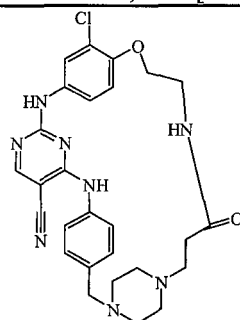
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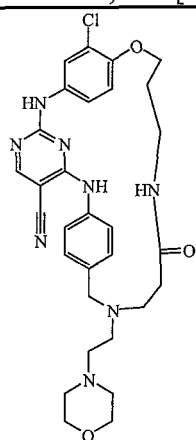
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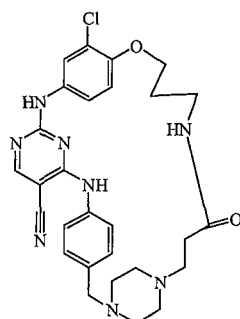
Co. No. 232; Ex. [B20]



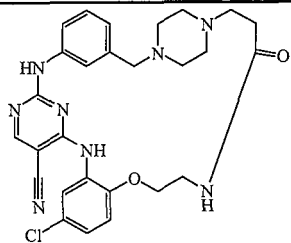
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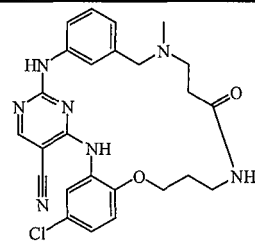
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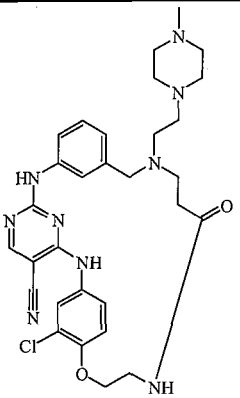
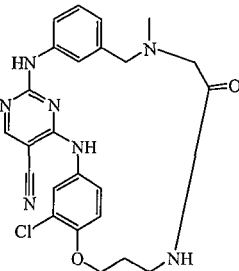
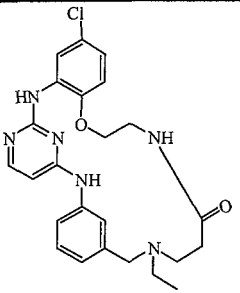
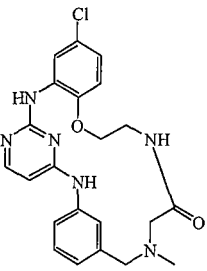
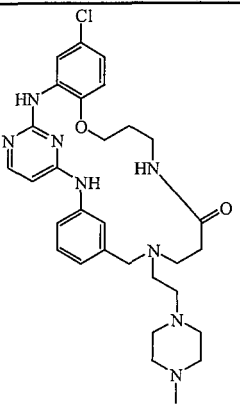
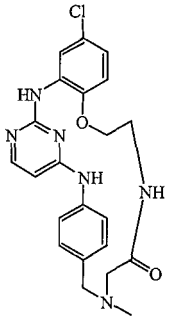
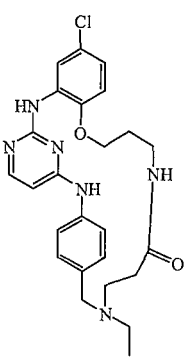
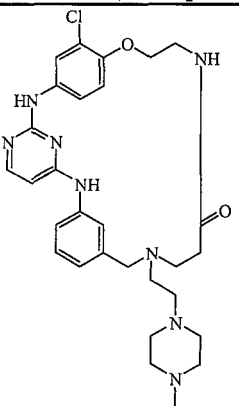
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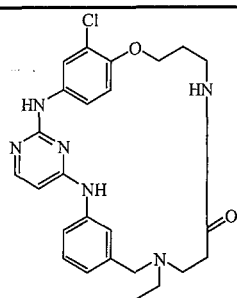


Co. No. 236; Ex. [B19]

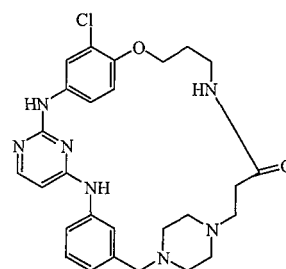


Co. No. 237; Ex. [B20]

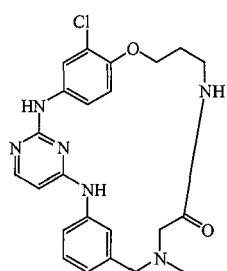
	
Co. No. 238; Ex. [B20]	Co. No. 239; Ex. [B20]
	
Co. No. 240; Ex. [B20]	Co. No. 241; Ex. [B20]
	
Co. No. 242; Ex. [B20]	Co. No. 243; Ex. [B20]
	
Co. No. 244; Ex. [B20]	Co. No. 245; Ex. [B20]



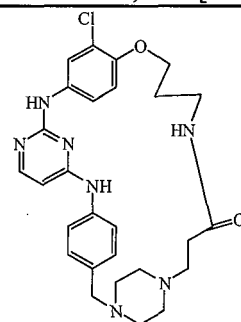
Co. No. 246; Ex. [B20]



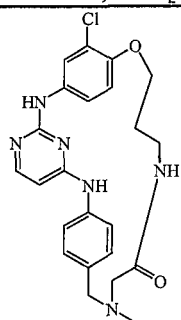
Co. No. 247; Ex. [B19]



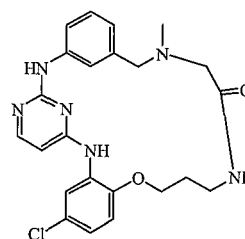
Co. No. 248; Ex. [B20]



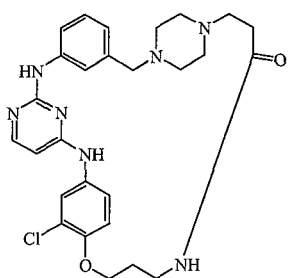
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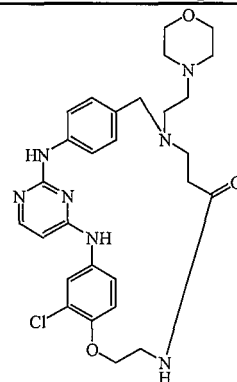
Co. No. 250; Ex. [B20]



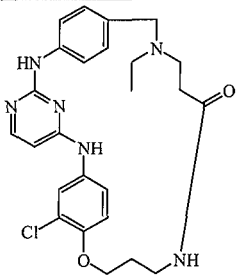
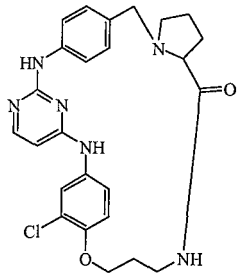
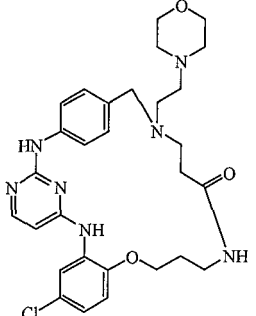
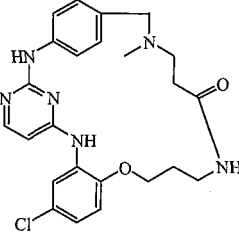
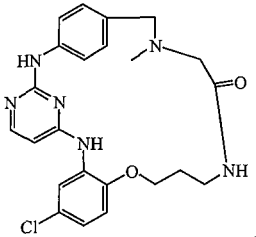
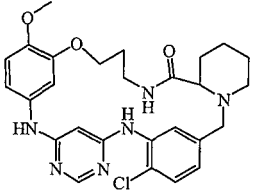
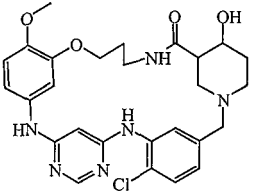
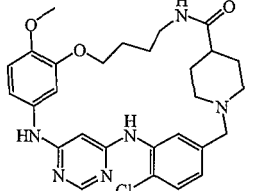
Co. No. 251; Ex. [B20]



Co. No. 252; Ex. [B19]



Co. No. 253; Ex. [B20]

	
Co. No. 254; Ex. [B20]	Co. No. 255; Ex. [B20]
	
Co. No. 256; Ex. [B20]	Co. No. 257; Ex. [B20]
	
Co. No. 258; Ex. [B20]	Co. No. 259; Ex. [B20]
	
Co. No. 260; Ex. [B20]	Co. No. 261; Ex. [B20]

Compound identification

LCMS-methods:

5

The HPLC gradient was supplied by a Waters Alliance HT 2790 system with a column heater set at 40°C. Flow from the column was split to a Waters 996 photodiode array (PDA) detector and a Waters-Micromass ZQ mass spectrometer with an electrospray ionization source operated in positive and negative ionization mode.

10

Method 1:

Reversed phase HPLC was carried out on a Xterra MS C18 column (3.5 mm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammoniumacetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 50% B and 50% C in 6.5 minutes, to 100 % B in 1 minute, 100% B for 1 minute and reequilibrate with 100 % A for 1.5 minutes. An injection volume of 10 uL was used.

15

Method 2:

Reversed phase HPLC was carried out on a Chromolith (4.6 x 25 mm) with a flow rate of 3 ml/min. Three mobile phases (mobile phase A 95% 25mM ammoniumacetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 96 % A to 2% B and 2% C in 0.9 minutes, to 49 % B and 49 % C in 0.3 minute, 100% B for 0.2 minute. An injection volume of 2 uL was used.

20

Method 3:

Reversed phase HPLC was carried out on a Xterra MS C18 column (3.5 mm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. Two mobile phases (mobile phase A methanol/H₂O; mobile phase B 0.1 % formic acid) were employed to run a gradient condition from 100 % B to 5 % B 12 minutes. An injection volume of 10 uL was used.

30

Method 4:

Reversed phase HPLC was carried out on a Xterra MS C18 column (3.5 mm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammoniumacetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a gradient condition from 100 % A to 30% A, 35 % B;

35

35 % C in 3 minutes to 50 % B and 50% C in 3.5 minutes, to 100 % B in 0.5 minute.
An injection volume of 10 uL was used.

Method 5:

- 5 Reversed phase HPLC was carried out on a Kromasil C18 column (3.5 mm, 4.6 x 100 mm) with a flow rate of 1 ml/min. Three mobile phases (mobile phase A ammoniumacetate; mobile phase B: acetonitrile; mobile phase C: formic acid) were employed to run a gradient condition from 30 % A, 40 % B, 30 % C for 1 minute to 100 % B for 5 minutes. An injection volume of 10 uL was used.

10

Method 6:

- Reversed phase HPLC was carried out on a Xterra MS C18 column (3.5 mm, 3.9 x 150 mm) with a flow rate of 1 ml/min. Three mobile phases (mobile phase A ammoniumacetate; mobile phase B: acetonitrile; mobile phase C: formic acid) were
15 employed to run a gradient condition from 85 % A, 15 % B for 3 minute to 80 % B for 6 minutes. An injection volume of 10 uL was used.

Table : retention time (RT in minutes) and molecular weight as the MH⁺

20

Co. No.	method LCMS	Rt	MH ⁺	Co. No.	method LCMS	Rt	MH ⁺
2	1	3.96	374	14	1	2.83	391
3	1	3.05	373	15	1	4.53	511
5	1	3.09	400	16	5	2.8	516
6	3	7.78	552	17	4	5.42	400
7	1	6.17	441	18	1	4.47	415
8	1	3.48	431	19	1	4.77	376
9	4	5.15	348	20	3	6.92	373
10	1	4.08	431	21	1	4.77	404
11	1	3.79	435	22	1	4.38	390
12	6	8.6	553	23	2	0.73	348
13	6	7.81	442	25	3	9.09	417

Co. No.	method LCMS	Rt	MH ⁺	Co. No.	method LCMS	Rt	MH ⁺
26	1	5.16	431	59	2	0.6	474
27	3	8.44	403	61	2	0.6	432
28	3	9.12	417	62	1	3.65	449
31	3	6.9	538	63	2	0.65	389
34	1	5.95	441	64	2	0.65	419
37	1	7.1	499	65	2	0.63	455
41	1	3.67	417	66	4	4.85	431
42	2	0.7	417	67	4	5.45	557
43	3	3.18	415	68	4	5.53	530
44	2	0.81	429	69	4	6.1	514
45	1	3.5	399	70	4	5.75	532
46	4	5.29	408	71	4	6.08	532
47	2	0.66	332	72	4	5.73	472
48	2	0.71	392	73	4	5.6	472
49	2	0.83	461	74	4	6.43	628
50	4	5.78	375	75	4	6.87	628
51	4	5.35	446	76	4	7.32	649
52	4	5.37	444	77	4	5.78	617
53	2	0.89	401	78	4	5.78	617
54	2	0.93	461	79	4	6.31	574
55	2	0.84	403	80	4	6.68	574
56	2	0.73	470	81	4	5.75	562
57	2	4.21	445	82	4	6.07	562
58	2	3.75	417	83	4	6.65	638

Co. No.	method LCMS	Rt	MH ⁺	Co. No.	method LCMS	Rt	MH ⁺
84	4	5.63	626	109	1	3.46	521
85	4	6.18	583	110	3	0.78	400
86	4	6.71	583	118	4	5.36	435
87	4	5.83	527	119	1	3.46	601
88	1	4.19	461	120	1	3.86	601
90	1	4.33	475	121	3	4.65	495
91	1	3.84	475	122	3	4.61	469
92	1	3.41	477	123	1	4.53	483
93	1	2.85	489	113	3	6.37	497
94	1	3.44	490	124	3	6.14	538
95	4	5.42	477	125	3	6.83	582
96	4	5.55	461	126	3	4.72	595
97	4	5.13	518	127	3	5.72	566
98	4	6.26	525	128	3	7.15	446
99	4	5.43	491	115	3	3.89	504
100	4	5.91	449	129	3	7.18	461
101	4	4.98	463	130	3	7.23	461
102	4	6.16	511	131	3	6.38	459
103	6	7.2	483	132	3	7.86	509
104	6	6.73	576	133	3	3.16	575
105	6	7.74	525	134	3	5.82	532
106	6	7.43	624	135	3	7.33	572
107	6	7.03	596	136	3	4.71	532
108	6	6.53	438	137	3	4.93	573

Co. No.	method LCMS	Rt	MH ⁺	Co. No.	method LCMS	Rt	MH ⁺
138	3	4.38	564	163	3	8.29	420
139	3	7.36	521	164	3	4.33	444
140	3	6.22	519	165	3	2.95	501
141	3	7.71	535	112	3	5.89	502
142	3	3.09	573	116	4	5.48	475
143	3	5.59	530	171	4	5.97	475
144	3	5.56	570	172	4	6.37	532
146	3	4.96	509	173	4	5.51	539
147	3	4.35	523	174	4	5.38	505
148	3	3.4	531	175	4	5.49	519
149	3	3.6	488	176	4	5.69	535
150	3	4.35	470	177	4	6.38	533
151	3	4.32	458	178	4	5.6	548
152	3	6.34	536	179	4	6.02	521
154	3	4.58	559	180	4	5.84	568
155	3	3.05	547	181	4	6.15	551
156	3	6.46	661	117	4	6.04	557
157	3	5.08	557	202	4	5.04	600
158	3	4.48	548	203	4	5.56	515
114	3	7.89	650	204	4	5.99	591
159	3	2.3	600	205	4	5.84	603
160	3	6.11	362	206	4	6.18	651
161	3	4.39	419	207	4	5.77	635
162	3	6.24	408	208	4	4.3	451

C. Pharmacological examples

The *in vitro* inhibition of a panel of kinases was assessed using either the glass-fiber
5 filter technology as described by Davies, S.P. et al., Biochem J. (2000), 351; p.95-105.

In the glass-fiber filter technology the activity of the kinase of interest is measured
using an appropriate substrate that is incubated with the aforementioned kinase protein
in the presence of (³³P) radiolabeled ATP. (³³P) Phosphorylation of the substrate is
10 subsequently measured as radioactivity bound on a glassfiber-filter.

Detailed description

All kinases are pre-diluted to a 10x working concentration prior to addition into the
15 assay. The composition of the dilution buffer for each kinase is detailed below.

Buffer Composition	Kinase(s)
50 mM Tris pH 7.5, 0.1 mM EGTA, 0.1 mM Na ₃ VO ₄ , 0.1% β-mercaptoethanol, 1 mg/ml BSA	CSK, Lyn
20 mM MOPS pH 7.0, 1 mM EDTA, 0.1% β-mercaptoethanol, 0.01% Brij-35, 5% glycerol, 1 mg/ml BSA	Abl, EGFR, Fes, Fms, Flt3, Fyn, GSK3β, Lck, Yes

All substrates are dissolved and diluted to working stocks in de-ionised water, apart
from histone H1 (10x working stock in 20 mM MOPS pH 7.4), PDKtide (10x working
20 stock in 50mM Tris pH 7.0) and ATF2 (which is typically stored at a 20x working
stock in 50 mM Tris pH 7.5, 150 mM NaCl, 0.1 mM EGTA, 0.03% Brij-35, 50%
glycerol, 1 mM benzamidine, 0.2 mM PMSF and 0.1% β-mercaptoethanol).

Example C.1: Abl human

25 In a final reaction volume of 25 μl, Abl (h) (5-10 mU) is incubated with 8 mM MOPS
pH 7.0, 0.2 mM EDTA, 50 μM EAIYAAPFAKKK, 10 mM MgAcetate and [γ-³³P-
ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The
reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes
at room temperature, the reaction is stopped by the addition of 5 μl of a 3% phosphoric

acid solution. 10 µl of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

5 Example C.2: CSK human

In a final reaction volume of 25 µl, CSK (h) (5-10 mU) is incubated with 50 mM Tris pH 7.5, 0.1 mM EGTA, 0.1 mM Na₃VO₄, 0.1% β-mercaptoethanol, 0.1 mg/ml poly(Glu, Tyr) 4:1, 10 mM MnCl₂, 10 mM MgAcetate and [γ-³³P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by
10 the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 µl of a 3% phosphoric acid solution. 10 µl of the reaction is then spotted onto a Filtermat A and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

15

Example C.3: cSRC human

In a final reaction volume of 25 µl, cSRC (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 µM KVEKIGEGTYGVVYK (Cdc2 peptide), 10 mM MgAcetate and [γ-³³P-ATP] (specific activity approx. 500 cpm/pmol,
20 concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 µl of a 3% phosphoric acid solution.
10 µl of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and
25 scintillation counting.

Example C.4: EGFR human

In a final reaction volume of 25 µl, EGFR (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 10mM MnCl₂, 0.1 mg/ml poly(Glu, Tyr) 4:1, 10 mM
30 MgAcetate and [γ-³³P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 µl of a 3% phosphoric acid solution. 10 µl of the reaction is then spotted onto a Filtermat A and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol
35 prior to drying and scintillation counting.

Example C.5: Fes human

In a final reaction volume of 25 μ l, Fes (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.1 mg/ml poly(Glu, Tyr) 4:1, 10 mM MgAcetate and [γ - 33 P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction is then spotted onto a Filtermat A and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

Example C.6: Flt3 human

In a final reaction volume of 25 μ l, Flt3 (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 50 μ M EAIYAAPFAKKK, 10 mM MgAcetate and [γ - 33 P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required).

The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

Example C.7: Fms human

In a final reaction volume of 25 μ l, Fms (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 μ M KKKSPGEYVNIEFG, 10 mM MgAcetate and [γ - 33 P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

Example C.8: GSK3 β human

In a final reaction volume of 25 μ l, GSK3 β (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 20 μ M YRRAAVPPSPSLSRHSSPHQS(p)EDEEE (phospho GS2 peptide), 10 mM MgAcetate and [γ - 33 P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction

is then spotted onto a P30 filtermat and washed three times for 5 minutes in 50 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

Example C.9: Lck human

- 5 In a final reaction volume of 25 μ l, Lck (h) (5-10 mU) is incubated with 50 mM Tris pH 7.5, 0.1 mM EGTA, 0.1 mM Na₃VO₄, 250 μ M KVEKIGEGTYGVVYK (Cdc2 peptide), 10 mM MgAcetate and [γ -³³P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the
- 10 addition of 5 μ l of a 3% phosphoric acid solution.
- 10 μ l of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

15 Example C.10: Lyn human

- In a final reaction volume of 25 μ l, Lyn (h) (5-10 mU) is incubated with 50 mM Tris pH 7.5, 0.1 mM EGTA, 0.1 mM Na₃VO₄, 0.1% β -mercaptoethanol, 0.1 mg/ml poly(Glu, Tyr) 4:1, 10 mM MgAcetate and [γ -³³P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the
- 20 MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction is then spotted onto a Filtermat A and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

25 Example C.11: Yes human

- In a final reaction volume of 25 μ l, Yes (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.1 mg/ml poly(Glu, Tyr) 4:1, 10 mM MgAcetate and [γ -³³P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room
- 30 temperature, the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction is then spotted onto a Filtermat A and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

- 35 The following tables provides the scores for the compounds according to the invention, obtained at a test concentration of 10⁻⁶ M using the above mentioned kinase assays.

Score 1 = 10-30% inhibition, Score 2 = 30-60% inhibition, Score 3 = 60-80% inhibition and Score 4 = > 80% inhibition.

Cpd No.	C1	C2	C3	C4	C4	C6	C7	C8	C9	C10	C11
103	4	2	4	4	3			1	4	4	4
12	2		4	4	2				4	4	4
36	2	1	1	4	1	1	1		2	3	1
37	2	1	1	3	1		1	1	2	2	1
39		1			1		1	1	1		
38		1	1	3			2	1		1	1
40				4		1		1	1		4
8	1	1		1			2			1	1
34		1	1	2	1	1	1		1	1	1
41					1			1		1	
57						2					
58		3				1	2			1	
60							1				1
61							3				1
109									1	1	1
108											1
35	4	1	1	2	1	2	2	1	2	2	3
42		2	1			2	2	1	2		3
43				2		2	2		1	2	1
13	1		1	4					2	4	4
105	4	2	4	4	3		1	1	4	4	4
106	4	3	4	4	4	1	1	1	4	4	4
107	4	3	4	4	4				4	4	4
27	1			1	1	3	2	2	2	1	1
28	1	1	2		1	3	2	3	2	1	3
25	1	2	1	1	3	4	2	2	2	1	1
2	1		2		1	4	2	3	2	1	2
20	1		1	1	1	2	1	3			1
29			1			4	1		2		3
26	1	1	1	1	2	3	2	1	1	2	1
3		1	1		1	2	2		1		1
18	1			1	1	2	2		1	2	1
21	1		1			3	2	1	2	1	1
19	1		1	1		2	1	1	2	1	2
5						1					
22	1	1	1		1	2	1		1	1	1
23	1				1	2					
31	2		2	2		2		1	3	4	4
6			1	1	1	2		2	2	1	2
4	1		2		2	4	3		2	1	2
24	2		1			3	1		2	1	1
32	3	1	4	4	4	4	1	4	4	4	4
33	3		4	3	2	4		2	3	4	4

Example C.12 : in vitro inhibition of EGFR (Flash Plate Assay)

- 5 The *in vitro* inhibition of EGFR was assessed using either the Flash Plate technology or the glass-fiber filter technology as described by Davies, S.P. et al., Biochem J. (2000),

351; p.95-105. The Flash Plate technology is generally described by B.A. Brown *et al.* in High Throughput Screening (1997), p.317-328. Editor(s): Devlin, John P. Publisher: Dekker, New York, N. Y.

- 5 In the Flash Plate EGFR kinase reaction assay, a kinase substrate consisting of biotinylated poly(L-glutamic acid-L-tyrosine) (poly(GT)biotin), is incubated with the aforementioned protein in the presence of (^{33}P) radiolabeled ATP. (^{33}P) phosphorylation of the substrate is subsequently measured as light energy emitted using a streptavidin-coated Flash Plate (PerkinElmer Life Sciences) by trapping and quantifying the binding
10 of the biotin tagged and radiolabeled substrate.

Detailed description

- The EGFR kinase reaction is performed at 30°C for 60 minutes in a 96-well microtiter FlashPlate (PerkinElmer Life Sciences). For each of the tested compounds a full dose
15 response 1.10^{-6}M to 1.10^{-10}M has been performed. IRESSA[®] and Tarceva[™] (erlotinib) were used as reference compounds. The 100 μl reaction volume contains 54.5 mM TrisHCl pH 8.0, 10 mM MgCl_2 , 100 μM Na_3VO_4 , 5.0 μM unlabeled ATP, 1mM DTT, 0.009% BSA, 0.8 μCi AT^{33}P , 0.35 $\mu\text{g/well}$ poly(GT)biotin and 0.5 μg EGFR-kinase domain/well.
20 The reaction is stopped by aspirating the reaction mixture and washing the plate 3x with 200 μl wash/stop buffer (PBS + 100 mM EDTA). After the final wash step 200 μl of wash/stop buffer was added to each well and the amount of phosphorylated (^{33}P) Poly(GT)biotin determined by counting (30 sec/well) in a microtiterplate scintillation counter.

- 25 In the glass-fiber filter technology EGFR kinase reaction assay, a kinase substrate consisting of poly(L-glutamic acid-L-tyrosine) (poly(GT)), is incubated with the aforementioned protein in the presence of (^{33}P) radiolabeled ATP. (^{33}P) Phosphorylation of the substrate is subsequently measured as radioactivity bound on a glassfiber-filter.

30

Detailed description

- The EGFR kinase reaction is performed at 25°C for 10 minutes in a 96-well microtiterplate. For each of the tested compounds a full dose response 1.10^{-6}M to 1.10^{-10}M has been performed. IRESSA[®] and Tarceva[™] (erlotinib) were used as reference
35 compounds. The 25 μl reaction volume contains 60 mM TrisHCl pH 7.5, 3 mM MgCl_2 , 3 mM Mn Cl_2 , 3 μM Na_3VO_4 , 50 $\mu\text{g/ml}$ PEG20000, 5.0 μM unlabeled ATP,

1mM DTT, 0.1 μ Ci AT³³P, 62.5 ng/well poly(GT) and 0.5 μ g EGFR-kinase domain/well.

The reaction is stopped by adding 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction mixture is then spotted onto a Filtermat A filter (Wallac) and washed 3 times
5 for 5 min. in 75 mM phosphoric acid and 1 time for 5 min. in methanol prior to drying and quantification on the Typhoon (Amersham) using a LE phosphorage storage screen.

Similarly to the above the *in vitro* inhibition of two other kinases, i.e human ErbB2 and
10 human ErbB4 was tested for some of the compounds according to the invention.

Example C.13 ErbB2 human

In a final reaction volume of 25 μ l, ErbB2 (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 10 mM MnCl₂, 0.1 mg/ml poly(Glu, Tyr) 4:1, 10 mM
15 MgAcetate and [γ -33P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction is then spotted onto a Filtermat A and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol
20 prior to drying and scintillation counting.

Example C.14 ErbB4 human

In a final reaction volume of 25 μ l, ErbB4 (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 10 mM MnCl₂, 0.1 mg/ml poly(Glu, Tyr) 4:1, 10 mM
25 MgAcetate and [γ -33P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 μ l of a 3% phosphoric acid solution. 10 μ l of the reaction is then spotted onto a Filtermat A and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol
30 prior to drying and scintillation counting.

The following tables provides the scores for the compounds according to the invention, obtained in these Flash Plate Assays. Score 1 = pIC₅₀ < 5, Score 2 = pIC₅₀ from 5 - 6, Score 3 = pIC₅₀ > 6.

Compound No	C12 EGFR-flash	C13 ERBB 2 Filter	C14 ERBB 4 Filter
	Score	Score	Score
112	3	3	3
114	3	2	
162	3	2	2
152	3	3	3
159	3	2	
148	3	2	2
158	3	2	
150	3	3	3
161	3	2	3
156	3	2	3
149	3	2	3
151	3	3	3
160	3	2	2
136	3		
180	2		
111	2		
182	2		
173	2		
113	2		
141	2		
196	2		
140	2		
145	2		
195	2		
179	2		
135	2		
190	2		
183	2		
186	2		
127	2		
154	2	2	
199			
119			
197			
126			
124			
122			
153		2	
163		3	
164		2	3
216			2

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions suitable for systemic administration to animal and human subjects in accordance with the present invention.

- 5 "Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable addition salt thereof.

Example D.1 : film-coated tablets

Preparation of tablet core

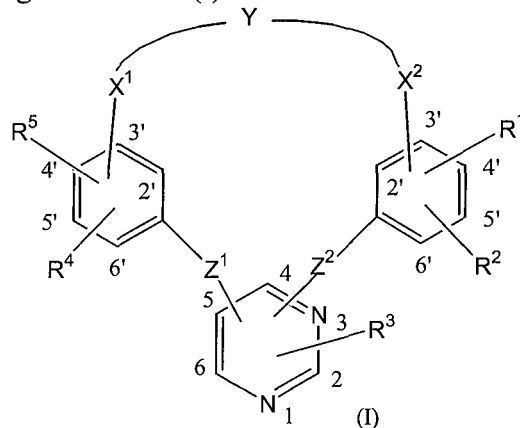
- 10 A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinyl-pyrrolidone (10 g) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline cellulose (100 g) and hydrogenated vegetable oil (15 g). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

- 15 To a solution of methyl cellulose (10 g) in denaturated ethanol (75 ml) there was added a solution of ethyl cellulose (5 g) in DCM (150 ml). Then there were added DCM (75 ml) and 1,2,3-propanetriol (2.5 ml). Polyethylene glycol (10 g) was molten and dissolved in dichloromethane (75 ml). The latter solution was added to the former and then there were
20 added magnesium octadecanoate (2.5 g), polyvinyl-pyrrolidone (5 g) and concentrated color suspension (30 ml) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Claims

1. A compound having the formula (I).



5

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

Z^1 and Z^2 each independently represents NR^{22} ; in particular Z^1 and Z^2 represents NH ;

Y represents $-C_{3-9}alkyl-$, $-C_{3-9}alkenyl-$, $-C_{3-9}alkynyl-$,

- 10 $-C_{3-7}alkyl-CO-NH-$ optionally substituted with amino, mono- or $di(C_{1-4}alkyl)amino$, aminosulfonyl, mono- or $di(C_{1-4}alkyl)aminosulfonyl$, $C_{1-4}alkylsulfide$, $C_{1-4}alkylsulfoxide$, $C_{1-4}alkylsulfide$ or $C_{1-4}alkyloxycarbonylamino-$,
 $-C_{3-7}alkenyl-CO-NH-$ optionally substituted with amino, mono- or $di(C_{1-4}alkyl)amino$, aminosulfonyl, mono- or $di(C_{1-4}alkyl)aminosulfonyl$,
 15 $C_{1-4}alkylsulfide$, $C_{1-4}alkylsulfoxide$, $C_{1-4}alkylsulfide$ or $C_{1-4}alkyloxycarbonylamino-$,
 $-C_{3-7}alkynyl-CO-NH-$ optionally substituted with amino, mono- or $di(C_{1-4}alkyl)amino$, aminosulfonyl, mono- or $di(C_{1-4}alkyl)aminosulfonyl$,
 $C_{1-4}alkylsulfide$, $C_{1-4}alkylsulfoxide$, $C_{1-4}alkylsulfide$ or $C_{1-4}alkyloxycarbonylamino-$,
 $-C_{1-5}alkyl-oxy-C_{1-5}alkyl-$, $-C_{1-5}alkyl-NR^6-C_{1-5}alkyl-$,
 20 $-C_{1-5}alkyl-NR^7-CO-C_{1-5}alkyl-$, $-C_{1-6}alkyl-CO-NH-$, $-C_{1-6}alkyl-NH-CO-$,
 $-C_{1-3}alkyl-NH-CS-Het^9-$, $-C_{1-3}alkyl-NH-CO-Het^3-$, $C_{1-2}alkyl-CO-Het^{10}-CO-$,
 $-Het^4-C_{1-3}alkyl-CO-NH-C_{1-3}alkyl-$, $-C_{1-7}alkyl-CO-$, $-C_{1-6}alkyl-CO-C_{1-6}alkyl-$,
 $-C_{1-2}alkyl-NH-CO-L^1-NH-$, $-NH-CO-L^2-NH-$, $-C_{1-2}alkyl-CO-NH-L^3-CO-$,
 $-C_{1-2}alkyl-NH-CO-L^1-NH-CO-C_{1-3}alkyl-$, $-C_{1-2}alkyl-NH-CO-L^1-NH-CO-$,
 25 $-CO-NH-L^2-CO-$, $-C_{1-2}alkyl-CO-NH-L^3-CO-NH-C_{1-3}alkyl-$,
 $-C_{1-2}alkyl-CO-NH-L^3-CO-NH-$, $-C_{1-2}alkyl-CO-NR^{10}-C_{1-3}alkyl-CO-$,
 $-C_{1-2}alkyl-NR^{11}-CH_2-CO-NH-C_{1-3}alkyl-$, $-NR^{12}-CO-C_{1-3}alkyl-NH-$,
 $Het^5-CO-C_{1-2}alkyl-$, $-C_{1-5}alkyl-CO-NH-C_{1-3}alkyl-CO-NH-$,

- C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-, -Het⁶-CO-Het⁷-, -Het⁸-NH-C₁₋₃alkyl-CO-NH-,
 -C₁₋₃alkyl-NH-CO-Het³²-CO-, or C₁₋₃alkyl-CO-Het³³-CO-NH-;
- X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹⁶,
 -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
- 5 X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹⁸,
 -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-, -Het²⁴-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
- R¹ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-,
 halo-phenyl-carbonylamino-, Het²⁰,
 C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-, or R¹ represents
- 10 C₁₋₆alkyl substituted with one or where possible two or more substituents selected
 from hydroxy, Het¹⁸ or halo;
- R² represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-,
 C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or
 di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-,
 15 aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide,
 C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- R³ represents hydrogen, cyano, nitro, C₁₋₄alkyl, or C₁₋₄alkyl substituted with one or
 more substituents selected from halo, C₁₋₄alkyloxy-, amino-, mono-or
 di(C₁₋₄alkyl)amino-, C₁₋₄alkyl-sulfonyl- or phenyl;
- 20 R⁴ represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-,
 C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or
 di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-,
 aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide,
 C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- 25 R⁵ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-,
 halo-phenyl-carbonylamino-, Het²¹,
 C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-, or R⁵ represents
 C₁₋₆alkyl substituted with one or where possible two or more substituents selected
 from hydroxy, Het¹⁹ or halo;
- 30 R⁶ represents hydrogen, C₁₋₄alkyl, Het¹¹, Het¹²-C₁₋₄alkyl- phenyl-C₁₋₄alkyl- or phenyl
 wherein said R⁶ is optionally substituted with one or where possible two or more
 substituents selected from hydroxy, amino or C₁₋₄alkyloxy-;
- R⁷ represents hydrogen, C₁₋₄alkyl, Het¹³-C₁₋₄alkyl- or C₁₋₄alkyloxyC₁₋₄alkyl-;
- R¹⁰, R¹² and R¹³ each independently represent hydrogen, or C₁₋₄alkyl optionally
 35 substituted with hydroxy, amino, mono- or di(C₁₋₄alkyl)amine, phenyl, Het²⁶ or
 C₁₋₄alkyloxy;

- R¹¹ represents hydrogen, C₁₋₄alkyl or represent mono-or di(C₁₋₄alkyl)amino-C₁₋₄alkyl-carbonyl- optionally substituted with hydroxy, pyrimidinyl, mono- or di(C₁₋₄alkyl)amine or C₁₋₄alkyloxy;
- R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl,
5 C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- R¹⁷ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, Het¹⁴, Het¹⁵-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- R²² represents hydrogen, C₁₋₄alkyl- optionally substituted with one or where possible two or three substituents selected from halo, cyano and phenyl;
- 10 L¹ represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, indolyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, cyano, thiazolyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, hydroxyphenyl, C₁₋₄alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amino-, imidazolyl or guanidino; in
15 particular L¹ represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, indolyl, pyridinyl, methylsulfide, hydroxy, thiol, cyano, thiazolyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, hydroxyphenyl, C₁₋₄alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amino-, imidazolyl or guanidino;
- 20 L² represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, indolyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, cyano, thiazolyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, hydroxyphenyl, C₁₋₄alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amine-, imidazolyl or guanidino; in
25 particular L² represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, indolyl, thienyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amino-, imidazolyl or guanidino;
- 30 L³ represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, indolyl, thienyl, pyridinyl, methylsulfide-, hydroxy, thiol, cyano, thiazolyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, hydroxyphenyl-, C₁₋₄alkyloxyphenyl-, aminocarbonyl-, hydroxycarbonyl-, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amino-, imidazolyl or guanidino; in
35 particular L³ represents C₁₋₈alkyl optionally substituted one ore where possible two or more substituents selected from phenyl, indolyl, thienyl, pyridinyl, methylsulfide-, hydroxy, thiol, cyano, hydroxyphenyl-, polyhaloC₁₋₄alkyl-phenyl-,

C₁₋₄alkyloxy-, aminocarbonyl-, hydroxycarbonyl-, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amino-, imidazolyl or guanidino;

Het¹ represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;

Het² represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het² is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;

Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;

Het⁵ and Het⁶ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁵ and Het⁶ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;

Het⁷ and Het⁸ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁷ and Het⁸ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;

Het⁹ and Het¹⁰ each independently represent a heterocycle selected from pyrrolidinyl, pyrrolyl, azetidiny, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁹ and Het¹⁰ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;

Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible

- two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 5 Het¹³ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 10 Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 15 Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 20 Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁶ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 25 Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 30 Het¹⁸ and Het¹⁹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹⁸ or Het¹⁹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- 35 Het²⁰ and Het²¹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het²⁰ or Het²¹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- 40 Het²² represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²² is optionally substituted with one or where possible

- two or more substituents selected from hydroxy, C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²⁵, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-; and
- Het²⁵ and Het²⁶ each independently represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²⁵ and Het²⁶ are optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl, pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het³² and Het³³ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-.
2. A compound of formula (I), wherein
- Z¹ and Z² each independently represents NR²²;
- Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₃₋₉alkynyl-, -C₃₋₇alkyl-CO-NH- optionally substituted with amino, mono- or di(C₁₋₄alkyl)amino, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₄alkyloxycarbonylamino-, -C₃₋₇alkenyl-CO-NH- optionally substituted with amino, mono- or di(C₁₋₄alkyl)amino, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₄alkyloxycarbonylamino-, -C₃₋₇alkynyl-CO-NH- optionally substituted with amino, mono- or di(C₁₋₄alkyl)amino, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₄alkyloxycarbonylamino-, -C₁₋₅alkyl-oxy-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-, -C₁₋₃alkyl-NH-CS-Het⁹-, -C₁₋₃alkyl-NH-CO-Het³-, C₁₋₂alkyl-CO-Het¹⁰-CO-, -Het⁴-CH₂-CO-NH-C₁₋₃alkyl-, -C₁₋₇alkyl-CO-, -C₁₋₆alkyl-CO-C₁₋₆alkyl-, -C₁₋₂alkyl-NH-CO-CR⁸R⁹-NH-, -C₁₋₂alkyl-CO-NH-CR²⁰R²¹-CO-, -C₁₋₂alkyl-NH-CO-CR²³R²⁴-NH-CO-, -C₁₋₂alkyl-CO-NH-CR²⁵R²⁶-CO-NH -C₁₋₂alkyl-CO-NR¹⁰-C₁₋₃alkyl-CO-, -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-,

- NR¹²-CO-C₁₋₃alkyl-NH-, Het⁵-CO-C₁₋₂alkyl-, -NH-CO-CR²⁷R²⁸-NH-C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-, -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-, -CO-NH-CR¹⁴R¹⁵-CO-, -Het⁶-CO-Het⁷-, or -Het⁸-NH-C₁₋₃alkyl-CO-NH-;
- 5 X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹⁶, -NR¹⁶-C₁₋₂alkyl-, -CH₂-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
- X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹⁸, -NR¹⁸-C₁₋₂alkyl-, -CH₂-, -CO-NR¹⁹-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
- 10 R¹ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-, halo-phenyl-carbonylamino-, Het²⁰, C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-, or R¹ represents C₁₋₆alkyl substituted with one or where possible two or more substituents selected from hydroxy, Het¹⁸ or halo;
- 15 R² represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- 20 R³ represents hydrogen, cyano, nitro, C₁₋₄alkyl, or C₁₋₄alkyl substituted with one or more substituents selected from halo, C₁₋₄alkyloxy-, amino-, mono-or di(C₁₋₄alkyl)amino-, C₁₋₄alkyl-sulfonyl- or phenyl;
- R⁴ represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- 25 R⁵ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-, halo-phenyl-carbonylamino-, Het²¹, C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-, or R⁵ represents C₁₋₆alkyl substituted with one or where possible two or more substituents selected from hydroxy, Het¹⁹ or halo;
- 30 R⁶ represents hydrogen, C₁₋₄alkyl, Het¹¹, Het¹²-C₁₋₄alkyl- phenyl-C₁₋₄alkyl- or phenyl wherein said R⁶ is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino or C₁₋₄alkyloxy-;
- 35 R⁷ represents hydrogen, C₁₋₄alkyl, Het¹³-C₁₋₄alkyl- or C₁₋₄alkyloxyC₁₋₄alkyl-;

- R^8 , R^9 , R^{23} and R^{24} each independently represents hydrogen or C_{1-4} alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, C_{1-4} alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C_{1-4} alkyl)-amine-, imidazolyl or guanidino;
- 5 R^{10} , R^{12} and R^{13} each independently represent hydrogen, or C_{1-4} alkyl optionally substituted with hydroxy, amino, mono- or di(C_{1-4} alkyl)amine, phenyl or C_{1-4} alkyloxy;
- R^{11} represents hydrogen, C_{1-4} alkyl or represent mono- or di(C_{1-4} alkyl)amino- C_{1-4} alkyl-carbonyl- optionally substituted with hydroxy, pyrimidinyl, mono- or
- 10 di(C_{1-4} alkyl)amine or C_{1-4} alkyloxy;
- R^{14} , R^{15} , R^{27} and R^{28} each independently represents hydrogen or C_{1-4} alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C_{1-4} alkyl)-amino-, imidazolyl or guanidino;
- 15 R^{16} and R^{18} each independently represent hydrogen, C_{1-4} alkyl, C_{1-4} alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷- C_{1-4} alkyl- or phenyl- C_{1-4} alkyl-;
- R^{17} and R^{19} each independently represent hydrogen, C_{1-4} alkyl, Het¹⁴, Het¹⁵- C_{1-4} alkyl- or phenyl- C_{1-4} alkyl-;
- R^{20} , R^{21} , R^{25} and R^{26} each independently represents hydrogen or C_{1-4} alkyl optionally
- 20 substituted with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C_{1-4} alkyl)-amino-, imidazolyl or guanidino;
- R^{22} represents hydrogen, C_{1-4} alkyl- optionally substituted with one or where possible two or three substituents selected from halo, cyano and phenyl;
- 25 Het¹ represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹ is optionally substituted with amino, C_{1-4} alkyl, hydroxy- C_{1-4} alkyl-, phenyl, phenyl- C_{1-4} alkyl-, C_{1-4} alkyl-oxy- C_{1-4} alkyl- mono- or di(C_{1-4} alkyl)amino- or amino-carbonyl-;
- 30 Het² represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het² is optionally substituted with amino, C_{1-4} alkyl, hydroxy- C_{1-4} alkyl-, phenyl, phenyl- C_{1-4} alkyl-, C_{1-4} alkyl-oxy- C_{1-4} alkyl- mono- or di(C_{1-4} alkyl)amino- or amino-carbonyl-;
- 35 Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or

- where possible two or more substituents selected from hydroxy, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het⁵ and Het⁶ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁵ and Het⁶ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het⁷ and Het⁸ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁷ and Het⁸ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het⁹ and Het¹⁰ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁹ and Het¹⁰ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹³ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹³ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁴ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁶ is optionally substituted with one or where possible two or more substituents

selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het¹⁸ and Het¹⁹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹⁸ or Het¹⁹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;

Het²⁰ and Het²¹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het²⁰ or Het²¹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;

Het²² represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said heterocycle is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²⁵, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-; and

Het²⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-.

3. A compound according to claim 1, wherein

Z¹ and Z² represents NH;

Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₃₋₇alkyl-CO-NH- optionally substituted with amino, mono- or di(C₁₋₄alkyl)amino or C₁₋₄alkyloxycarbonylamino-; -C₁₋₅alkyl-oxy-C₁₋₅alkyl-; -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-;

- C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-; -C₁₋₆alkyl-CO-NH-; -C₁₋₆alkyl-NH-CO-;
 -C₁₋₃alkyl-NH-CS-Het⁹-; -C₁₋₃alkyl-NH-CO-Het³-; C₁₋₂alkyl-CO-Het¹⁰-CO-;
 -Het⁴-CH₂-CO-NH-C₁₋₃alkyl-; -C₁₋₇alkyl-CO-; -C₁₋₆alkyl-CO-C₁₋₆alkyl-;
 -C₁₋₂alkyl-NH-CO-L¹-NH-; -C₁₋₂alkyl-CO-NH-L³-CO-; -CO-NH-L²-CO-;
 5 -C₁₋₂alkyl-NH-CO-L¹-NH-CO-; -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-CO-;
 -C₁₋₂alkyl-CO-NR¹⁰-C₁₋₃alkyl-CO-; -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-;
 -NR¹²-CO-C₁₋₃alkyl-NH-; Het⁵-CO-C₁₋₂alkyl-; -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-;
 ; -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-; -Het⁶-CO-Het⁷-; -Het⁸-NH-C₁₋₃alkyl-CO-NH-;
 C₁₋₃alkyl-NH-CO-Het³²-CO- or C₁₋₃alkyl-CO-Het³³-CO-NH-;
 10 X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-, NR¹⁶,
 -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-, NR¹⁸,
 -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-, -Het²⁴-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 R¹ represents hydrogen, halo, C₁₋₆alkoxy-, Het²⁰ or R¹ represents
 15 C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkoxy-;
 R² represents hydrogen, halo or hydroxy;
 R³ represents hydrogen, nitro or cyano;
 R⁴ represents hydrogen or halo;
 R⁵ represents hydrogen, halo, C₁₋₆alkoxy-, Het²¹ or R⁵ represents
 20 C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkoxy-;
 R⁶ represents hydrogen;
 R⁷ represents hydrogen, C₁₋₄alkyl, or Het¹³-C₁₋₄alkyl-;
 R⁸ and R⁹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted
 with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or di(C₁₋₄alkyl)-amino-
 25 or imidazolyl;
 R¹⁰, R¹² and R¹³ each independently represent hydrogen or C₁₋₄alkyl optionally
 substituted with hydroxy or C₁₋₄alkoxy-;
 R¹¹ represents hydrogen, or C₁₋₄alkyl;
 R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl,
 30 C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
 R¹⁷ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, Het¹⁴, Het¹⁵-C₁₋₄alkyl- or
 phenyl-C₁₋₄alkyl-;
 L¹ represents C₁₋₈alkyl optionally substituted one or where possible two or more
 substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol,
 35 thiazolyl, cyano, hydroxyphenyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkoxy-,
 C₁₋₄alkoxyphenyl-, aminocarbonyl, C₃₋₆cycloalkyl, amino, mono- or
 di(C₁₋₄alkyl)-amine-, or imidazolyl;

- L² represents C₁₋₈alkyl optionally substituted one or where possible two or more substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, thiazolyl, cyano, hydroxyphenyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, C₁₋₄alkyloxyphenyl-, aminocarbonyl, C₃₋₆cycloalkyl, amino, mono- or
5 di(C₁₋₄alkyl)-amine-, or imidazolyl;
- L³ represents C₁₋₈alkyl optionally substituted one or where possible two or more substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, thiazolyl, cyano, hydroxyphenyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, C₁₋₄alkyloxyphenyl-, aminocarbonyl, C₃₋₆cycloalkyl, amino, mono- or
10 di(C₁₋₄alkyl)-amine-, or imidazolyl;
- Het¹ and Het² each independently represent morpholinyl or pyridinyl, wherein said Het¹ or Het² are optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl-, mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- 15 Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or where possible two or more hydroxy or Het²²-carbonyl- substituents;
- Het⁵ and Het⁶ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁵ and Het⁶ are
20 optionally substituted with one or where possible two or more hydroxy substituents;
- Het⁷ and Het⁸ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁷ and Het⁸ are
25 optionally substituted with one or where possible two or more hydroxy substituents;
- Het⁹ and Het¹⁰ each independently represent a heterocycle selected from pyrrolidinyl, pyrrolyl, azetidiny, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁹ and Het¹⁰ are optionally substituted with one or where possible two or more
30 hydroxy or C₁₋₄alkyl substituents;
- Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 35 Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible

- two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹³ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl are optionally substituted with one or where possible
 5 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl are optionally substituted with one or where possible
 10 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible
 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 15 Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁶ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or
 20 piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het²⁰ and Het²¹ each independently represent morpholinyl or pyridinyl;
 Het²² represents piperazinyl optionally substituted with C₁₋₄alkyl or hydroxy;
- 25 Het²³ and Het²⁴ each independently represent pyrrolidinyl, decahydroquinolinyl or piperidinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²²-carbonyl- or C₁₋₄alkyl-;
- Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl,
 30 pyrrolidinyl or piperidinyl.

4. A compound according to claims 1 or 3 wherein;

Z¹ and Z² represents NH;

Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-,

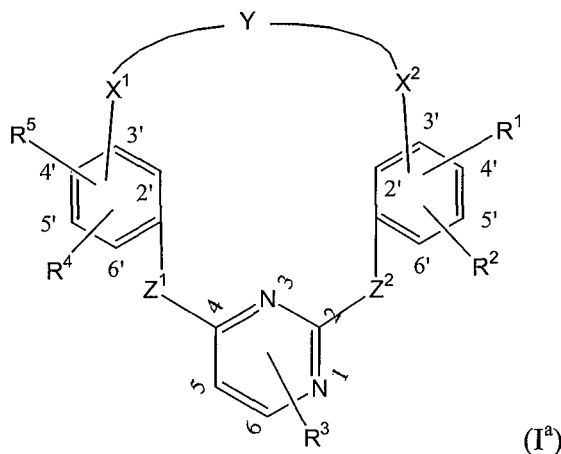
- 35 -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-,
 -C₁₋₂alkyl-CO-Het¹⁰-CO-, -C₁₋₃alkyl-NH-CO-Het³-,

- Het⁴-C₁₋₃alkyl-CO-NH-C₁₋₃alkyl-, -C₁₋₂alkyl-NH-CO-L¹-NH-, -NH-CO-L²-NH-,
 -C₁₋₂alkyl-CO-NH-L³-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-,
 -C₁₋₂alkyl-CO-NH-L³-CO-NH-C₁₋₃alkyl-, -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-,
 Het⁵-CO-C₁₋₂alkyl-, -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-,
 5 -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-, -C₁₋₃alkyl-NH-CO-Het³²-CO-, or
 -C₁₋₃alkyl-CO-Het³³-CO-NH-;
 X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁶-C₁₋₂alkyl-,
 -CO-NR¹⁷-, Het²³-C₁₋₂alkyl- or C₁₋₂alkyl;
 X² represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl-,
 10 -CO-NR¹⁹-, Het²⁴-C₁₋₂alkyl- or C₁₋₂alkyl;
 R¹ represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het¹ or
 C₁₋₄alkyloxy-;
 R² represents hydrogen or halo;
 R³ represents hydrogen or cyano;
 15 R⁴ represents hydrogen or halo;
 R⁵ represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het² or
 C₁₋₄alkyloxy-;
 R⁶ represents hydrogen;
 R⁷ represents hydrogen;
 20 R¹¹ represents hydrogen or C₁₋₄alkyl;
 R¹³ represents hydrogen;
 R¹⁶ and R¹⁸ represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl;
 R¹⁷ and R¹⁹ represent hydrogen;
 L¹ represents C₁₋₈alkyl optionally substituted with one or where possible two or more
 25 substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-,
 C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;
 L² represents C₁₋₈alkyl optionally substituted with one or where possible two or more
 substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-,
 C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;
 30 L³ represents C₁₋₈alkyl optionally substituted with one or where possible two or more
 substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-,
 C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;
 Het¹ represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het¹
 represents morpholinyl or piperazinyl; more in particular Het¹ represents
 35 morpholinyl;

- Het² represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het² represents morpholinyl or piperazinyl; more in particular Het² represents morpholinyl;
- Het³ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl; in particular Het³ represents piperazinyl, piperidinyl or pyrrolidinyl;
- Het⁴ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl; in particular Het⁴ represents piperazinyl or piperidinyl;
- Het⁵ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl, in particular Het⁵ represents piperazinyl or piperidinyl, more in particular Het⁵ represents piperazinyl;
- Het¹⁰ represents piperazinyl, piperidinyl, pyrrolidinyl or azetidyl; in particular Het¹⁰ represents pyrrolidinyl, piperazinyl or azetidyl, more in particular Het¹⁰ represents azetidyl;
- Het¹⁷ represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl; in particular Het¹⁷ represents morpholinyl or piperazinyl;
- Het²² represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl wherein said Het²² is optionally substituted with C₁₋₄alkyl; in particular Het²² represents morpholinyl or piperazinyl wherein said morpholinyl or piperazinyl or optionally substituted with C₁₋₄alkyl; more in particular Het²² represents piperazinyl optionally substituted with C₁₋₄alkyl;
- Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ are optionally substituted with Het²²-carbonyl;
- Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl, in particular Het³² and Het³³ are each independently selected from morpholinyl, piperazinyl or piperidinyl, more in particular Het³² and Het³³ are each independently selected from morpholinyl or piperidinyl.
5. A compound according to any one of claims 1 to 4 wherein the X² substituent is at position 3', the R¹ substituent represents hydrogen or halo and is at position 4', the R² substituent represents halo and is at position 5', the X¹ substituent is at position 3', the R⁵ substituent is at position 4' and represents hydrogen or C₁₋₄alkyloxy- and the R⁴ substituent at position 5' of the structure of formula (I).
6. A compound according to any one of claims 1 to 4 wherein the X² substituent is at position 2', the R¹ substituent represents hydrogen or halo and is at position 4', the

R^2 substituent represents halo and is at position 5', the X^1 substituent is at position 3', the R^5 substituent is at position 4' and represents hydrogen or C_{1-4} alkyloxy- and the R^4 substituent at position 5' of the structure of formula (I).

- 5 7. A compound according to any one of claims 1 to 6 for use as a medicine.
8. Use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for treating hyper proliferative disorders such as atherosclerosis, restenosis and cancer.
- 10 9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective kinase inhibitory amount of a compound as described in any one of the claims 1 to 6.
- 15 10. A compound having the formula (I^a)



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

Z^1 and Z^2 each independently represents NR^{22} ;

- 20 Y represents $-C_{3-9}$ alkyl-, $-C_{3-9}$ alkenyl-, $-C_{3-9}$ alkynyl-,
 $-C_{3-7}$ alkyl-CO-NH- optionally substituted with amino, mono- or di(C_{1-4} alkyl)amino,
 aminosulfonyl, mono- or di(C_{1-4} alkyl)aminosulfonyl, C_{1-4} alkylsulfide,
 C_{1-4} alkylsulfoxide, C_{1-4} alkylsulfide or C_{1-4} alkyloxycarbonylamino-,
 $-C_{3-7}$ alkenyl-CO-NH- optionally substituted with amino, mono- or
 di(C_{1-4} alkyl)amino, aminosulfonyl, mono- or di(C_{1-4} alkyl)aminosulfonyl,
 C_{1-4} alkylsulfide, C_{1-4} alkylsulfoxide, C_{1-4} alkylsulfide or C_{1-4} alkyloxycarbonylamino-,
 25 $-C_{3-7}$ alkynyl-CO-NH- optionally substituted with amino, mono- or

- di(C₁₋₄alkyl)amino, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₄alkyloxycarbonylamino-, -C₁₋₅alkyl-oxy-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-, -C₁₋₃alkyl-NH-CS-Het⁹-, -C₁₋₃alkyl-NH-CO-Het³-, C₁₋₂alkyl-CO-Het¹⁰-CO-, -Het⁴-CH₂-CO-NH-C₁₋₃alkyl-, -C₁₋₇alkyl-CO-, -C₁₋₆alkyl-CO-C₁₋₆alkyl-, -C₁₋₂alkyl-NH-CO-CR⁸R⁹-NH-, -C₁₋₂alkyl-CO-NH-CR²⁰R²¹-CO-, -C₁₋₂alkyl-CO-NR¹⁰-C₁₋₃alkyl-CO-, -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-, -NR¹²-CO-C₁₋₃alkyl-NH-, Het⁵-CO-C₁₋₂alkyl-, -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-, -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-, -CO-NH-CR¹⁴R¹⁵-CO-, -Het⁶-CO-Het⁷-, or -Het⁸-NH-C₁₋₃alkyl-CO-NH- ;
- X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹⁶, -NR¹⁶-C₁₋₂alkyl-, -CH₂-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
- X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO-C₁₋₂alkyl-, NR¹⁸, -NR¹⁸-C₁₋₂alkyl-, -CH₂-, -CO-NR¹⁹-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
- R¹ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-, halo-phenyl-carbonylamino-, Het²⁰, C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-, or R¹ represents C₁₋₆alkyl substituted with one or where possible two or more substituents selected from hydroxy, Het¹⁸ or halo;
- R² represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- R³ represents hydrogen, cyano, nitro, C₁₋₄alkyl, or C₁₋₄alkyl substituted with one or more substituents selected from halo, C₁₋₄alkyloxy-, amino-, mono-or di(C₁₋₄alkyl)amino-, C₁₋₄alkyl-sulfonyl- or phenyl;
- R⁴ represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- R⁵ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-, halo-phenyl-carbonylamino-, Het²¹,

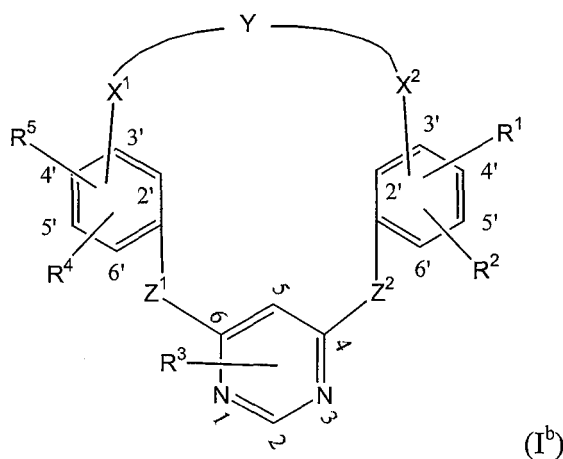
- C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-, or R⁵ represents C₁₋₆alkyl substituted with one or where possible two or more substituents selected from hydroxy, Het¹⁹ or halo;
- R⁶ represents hydrogen, C₁₋₄alkyl, Het¹¹, Het¹²-C₁₋₄alkyl-, phenyl-C₁₋₄alkyl or phenyl
5 optionally substituted with one or where possible two or more substituents selected from hydrogen, hydroxy, amino or C₁₋₄alkyloxy-;
- R⁷ represents hydrogen, C₁₋₄alkyl, Het¹³-C₁₋₄alkyl- or C₁₋₄alkyloxyC₁₋₄alkyl-;
- R⁸ and R⁹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl,
10 C₁₋₄alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amino-, imidazolyl or guanidino;
- R¹⁰, R¹² and R¹³ each independently represent hydrogen or C₁₋₄alkyl optionally substituted with hydroxy or C₁₋₄alkyloxy;
- R¹¹ represents hydrogen, C₁₋₄alkyl or represent
15 mono-or di(C₁₋₄alkyl)amino-C₁₋₄alkyl-carbonyl- optionally substituted with hydroxy, pyrimidinyl, dimethylamine or C₁₋₄alkyloxy;
- R¹⁴ and R¹⁵ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amino-,
20 imidazolyl or guanidino;
- R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- R¹⁷ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, Het¹⁴, Het¹⁵-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- 25 R²⁰ and R²¹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amino-, imidazolyl or guanidino;
- R²² represents hydrogen, C₁₋₄alkyl- optionally substituted with one or where possible
30 two or three substituents selected from halo, cyano and phenyl;
- Het¹ represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-,
35 C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- Het² represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl,

- oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het² is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- 5 Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- 10 Het⁵ and Het⁶ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁵ and Het⁶ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- 15 Het⁷ and Het⁸ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁷ and Het⁸ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- 20 Het⁹ and Het¹⁰ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁹ and Het¹⁰ are optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- 25 Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 30 Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 35 Het¹³ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹³ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁴ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

- Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 5 Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁶ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 10 Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 15 Het¹⁸ and Het¹⁹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹⁸ or Het¹⁹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- 20 Het²⁰ and Het²¹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het²⁰ or Het²¹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- 25 Het²² represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 30 Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²⁵, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-; and
- 35 Het²⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-.

11. A compound according to claim 10 wherein
 Z^1 and Z^2 represents NH;
Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₁₋₆alkyl-CO-NH-,
5 -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₃alkyl-NH-CO-Het³- or -C₁₋₂alkyl-NR¹¹-CH₂-
CO-NH-C₁₋₃alkyl-;
 X^1 represents a direct bond, O, -O-C₁₋₂alkyl-, -NR¹⁶-C₁₋₂alkyl-, Het²³-C₁₋₂alkyl or
-CO-NR¹⁷-;
 X^2 represents a direct bond, O, -O-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl-, Het²⁴-C₁₋₂alkyl or
10 -CO-NR¹⁹-;
 R^1 represents hydrogen, halo, C₁₋₆alkoxy-, or R^1 represents
C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-;
 R^2 represents hydrogen or halo;
 R^3 represents hydrogen, or cyano;
15 R^4 represents hydrogen or halo;
 R^5 represents hydrogen, halo, C₁₋₆alkoxy-, or R^5 represents
C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-;
 R^7 represents hydrogen;
 R^{11} represents hydrogen or C₁₋₄alkyl-;
20 R^{16} and R^{18} each independently represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl-;
 R^{17} represents hydrogen;
 R^{19} represents hydrogen;
Het³ represents pyrrolidinyl;
Het¹⁷ represents morpholinyl or piperazinyl wherein said Het¹⁷ is optionally substituted
25 with C₁₋₄alkyl-;
Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl
or piperazinyl.
12. A compound according to claims 10 or 11 wherein
30 Z^1 and Z^2 represents NH;
Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-NH-
CO-, -C₁₋₃alkyl-NH-CO-Het³- or -C₁₋₂alkyl-NR¹¹-CH₂CO-NH-C₁₋₃alkyl-;
 X^1 represents a direct bond, O, -NR¹⁶-C₁₋₂alkyl- or C₁₋₂alkyl-;
 X^2 represents a direct bond, O, -NR¹⁸-C₁₋₂alkyl- or C₁₋₂alkyl-;
35 R^1 represents hydrogen, halo or C₁₋₆alkyloxy-;
 R^2 represents hydrogen or halo;
 R^3 represents hydrogen or cyano;

- R^4 represents hydrogen or halo;
 R^5 represents hydrogen, halo or C_{1-6} alkyloxy-;
 R^6 represents hydrogen;
 R^7 represents hydrogen;
 R^{11} represents hydrogen or C_{1-4} alkyl;
 R^{16} and R^{18} represent hydrogen; and
 R^{17} and R^{19} represent hydrogen;
 Het³ represents pyrrolidinyl.
13. A compound according to any one of claims 10 to 12 for use as a medicine.
14. Use of a compound according to any one of claims 10 to 12 in the manufacture of a medicament for treating hyper proliferative disorders such as atherosclerosis, restenosis and cancer.
15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective kinase inhibitory amount of a compound as described in any one of the claims 10 to 12.
16. A compound having the fomula (I^b)



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

Z^1 and Z^2 represents NH;

- Y represents $-C_{3-9}$ alkyl-, $-C_{3-9}$ alkenyl-, $-C_{3-7}$ alkyl-CO-NH- optionally substituted with amino, mono- or di(C_{1-4} alkyl)amino or C_{1-4} alkyloxycarbonylamino-, $-C_{1-5}$ alkyl-oxy- C_{1-5} alkyl-, $-C_{1-5}$ alkyl-NR⁶- C_{1-5} alkyl-,

- C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-,
 -C₁₋₃alkyl-NH-CS-Het⁹-, -C₁₋₃alkyl-NH-CO-Het³-, C₁₋₂alkyl-CO-Het¹⁰-CO-,
 -Het⁴-CH₂-CO-NH-C₁₋₃alkyl-, -C₁₋₇alkyl-CO-, -C₁₋₆alkyl-CO-C₁₋₆alkyl-,
 -C₁₋₂alkyl-NH-CO-L¹-NH-, -C₁₋₂alkyl-CO-NH-L³-CO-, -CO-NH-L²-CO-,
 5 -C₁₋₂alkyl-NH-CO-L¹-NH-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-CO-,
 -C₁₋₂alkyl-CO-NR¹⁰-C₁₋₃alkyl-CO-, -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-,
 -NR¹²-CO-C₁₋₃alkyl-NH-, Het⁵-CO-C₁₋₂alkyl-, -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-,
 -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-, -Het⁶-CO-Het⁷-, -Het⁸-NH-C₁₋₃alkyl-CO-NH-,
 C₁₋₃alkyl-NH-CO-Het³²-CO-, or C₁₋₃alkyl-CO-Het³³-CO-NH-;
- 10 X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-, NR¹⁶,
 -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 in particular X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-,
 NR¹⁶, -NR¹⁶-C₁₋₂alkyl-, -CO-NR¹⁷-, -Het²³-, -Het²³-C₁₋₂alkyl-, -O-N=CH- or
 -C₁₋₂alkyl-;
- 15 X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-, NR¹⁸,
 -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-, -Het²⁴-C₁₋₂alkyl-, -O-N=CH- or -C₁₋₂alkyl-;
 in particular X² represents a direct bond, O, -O-C₁₋₂alkyl-, CO, -CO- C₁₋₂alkyl-,
 NR¹⁸, -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, -Het²⁴-, -Het²⁴-C₁₋₂alkyl-, -O-N=CH- or
 -C₁₋₂alkyl-;
- 20 R¹ represents hydrogen, halo, C₁₋₆alkoxy-, Het²⁰ or R¹ represents
 C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-; in particular R¹ represents
 hydrogen halo or C₁₋₄alkyloxy-;
- R² represents hydrogen, halo or hydroxy; in particular R² represents hydrogen or halo;
 R³ represents hydrogen, nitro or cyano; in particular R³ represents hydrogen or cyano;
- 25 R⁴ represents hydrogen or halo;
 R⁵ represents hydrogen, halo, C₁₋₆alkoxy-, Het²¹ or R⁵ represents
 C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-; in particular R⁵ represents
 hydrogen, halo or C₁₋₆alkyloxy-;
- R⁶ represents hydrogen;
- 30 R⁷ represents hydrogen, C₁₋₄alkyl, or Het¹³-C₁₋₄alkyl-; in particular R⁷ represents
 hydrogen or Het¹³-C₁₋₄alkyl-;
- R⁸ and R⁹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted
 with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or di(C₁₋₄alkyl)-amino-
 or imidazolyl; in particular R⁷ represents hydrogen, C₁₋₄alkyl, or Het¹³-C₁₋₄alkyl-;
- 35 even more particular R⁷ represents hydrogen or Het¹³-C₁₋₄alkyl-;

- R¹⁰, R¹² and R¹³ each independently represent hydrogen or C₁₋₄alkyl optionally substituted with hydroxy or C₁₋₄alkyloxy; in particular R¹³ represents hydrogen, or C₁₋₄alkyl;
- R¹¹ represents hydrogen, or C₁₋₄alkyl;
- 5 R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl, C₁₋₄alkyl-oxy-carbonyl-, Het¹⁶, Het¹⁷-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- R¹⁷ and R¹⁹ each independently represent hydrogen, C₁₋₄alkyl, Het¹⁴, Het¹⁵-C₁₋₄alkyl- or phenyl-C₁₋₄alkyl-;
- L¹ represents C₁₋₈alkyl optionally substituted one ore where possible two or more
10 substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, thiazolyl, cyano, hydroxyphenyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, C₁₋₄alkyloxyphenyl-, aminocarbonyl, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amine-, or imidazolyl;
- L² represents C₁₋₈alkyl optionally substituted one ore where possible two or more
15 substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, thiazolyl, cyano, hydroxyphenyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, C₁₋₄alkyloxyphenyl-, aminocarbonyl, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amine-, or imidazolyl;
- L³ represents C₁₋₈alkyl optionally substituted one ore where possible two or more
20 substituents selected from phenyl, thienyl, pyridinyl, methylsulfide, hydroxy, thiol, thiazolyl, cyano, hydroxyphenyl, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy-, C₁₋₄alkyloxyphenyl-, aminocarbonyl, C₃₋₆cycloalkyl, amino, mono- or di(C₁₋₄alkyl)-amine-, or imidazolyl;
- Het¹ and Het² each independently represent morpholinyl pyridinyl, wherein said Het¹
25 or Het² are optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-; in particular Het¹ and Het² each independently represent morpholinyl;
- Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-
30 pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or where possible two or more hydroxy or Het²²-carbonyl- substituents; in particular Het³ and Het⁴ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl,
35 piperazinyl or piperidinyl wherein said Het³ and Het⁴ are optionally substituted with one or where possible two or more hydroxy substituents;

- Het⁵ and Het⁶ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁵ and Het⁶ are optionally substituted with one or where possible two or more hydroxy substituents;
- 5 Het⁷ and Het⁸ each independently represent a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁷ and Het⁸ are optionally substituted with one or where possible two or more hydroxy substituents;
- 10 Het⁹ and Het¹⁰ each independently represent a heterocycle selected from pyrrolidinyl, pyrrolyl, azetidiny, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het⁹ and Het¹⁰ are optionally substituted with one or where possible two or more hydroxy or C₁₋₄alkyl substituents;
- 15 Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 20 Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 25 Het¹³ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl are optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 30 Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperidinyl are optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 35 Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁶ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹⁶ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

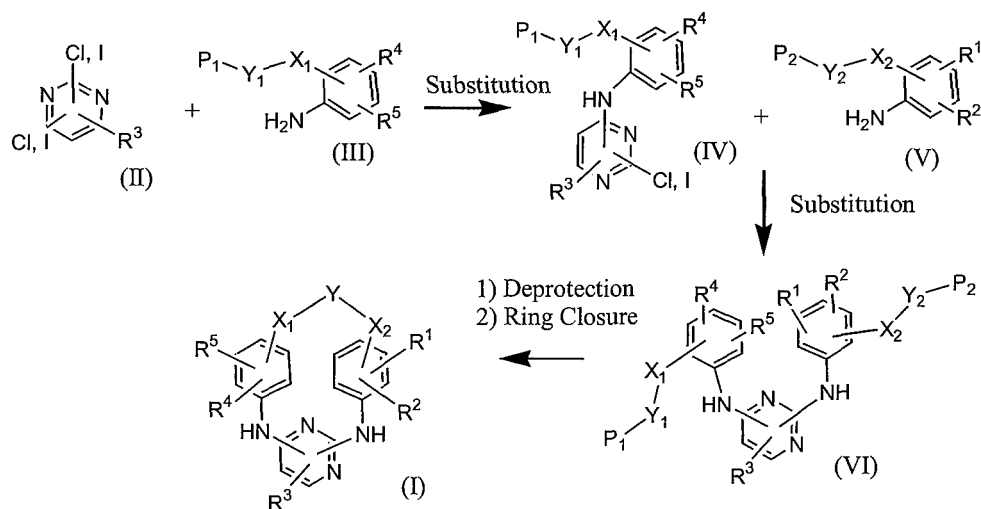
- Het¹⁷ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁷ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 5 Het²⁰ and Het²¹ each independently represent morpholinyl or pyridinyl;
- Het²² represents piperazinyl or piperidinyl optionally substituted with C₁₋₄alkyl or hydroxy;
- Het²³ and Het²⁴ each independently represent pyrrolidinyl, decahydroquinolinyl or piperidinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²²-carbonyl- or C₁₋₄alkyl; in particular Het²³ and Het²⁴ each independently represent pyrrolidinyl, decahydroquinolinyl or pyridinyl wherein said Het²³ or Het²⁴ is optionally substituted with one or where possible two or more substituents selected from hydroxy or C₁₋₄alkyl;
- 10
- 15 Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl, pyrrolidinyl or piperidinyl.

17. A compound according to claim 16 wherein,
- Z¹ and Z² represents NH;
- 20 Y represents -C₃₋₉alkyl-, -C₃₋₉alkenyl-, -C₁₋₅alkyl-NR⁶-C₁₋₅alkyl-, -C₁₋₅alkyl-NR⁷-CO-C₁₋₅alkyl-, -C₁₋₆alkyl-CO-NH-, -C₁₋₆alkyl-NH-CO-, -C₁₋₂alkyl-CO-Het¹⁰-CO-, -C₁₋₃alkyl-NH-CO-Het³-, -Het⁴-C₁₋₃alkyl-CO-NH-C₁₋₃alkyl-, -C₁₋₂alkyl-NH-CO-L¹-NH-, -NH-CO-L²-NH-, -C₁₋₂alkyl-CO-NH-L³-CO-, -C₁₋₂alkyl-NH-CO-L¹-NH-CO-C₁₋₃alkyl-, -C₁₋₂alkyl-
- 25 CO-NH-L³-CO-NH-C₁₋₃alkyl-, -C₁₋₂alkyl-NR¹¹-CH₂-CO-NH-C₁₋₃alkyl-, Het⁵-CO-C₁₋₂alkyl-, -C₁₋₅alkyl-CO-NH-C₁₋₃alkyl-CO-NH-, -C₁₋₅alkyl-NR¹³-CO-C₁₋₃alkyl-NH-, -C₁₋₃alkyl-NH-CO-Het³²-CO-, or -C₁₋₃alkyl-CO-Het³³-CO-NH-;
- X¹ represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁶-C₁₋₂alkyl-,
- 30 -CO-NR¹⁷-, Het²³-C₁₋₂alkyl- or C₁₋₂alkyl;
- X² represents a direct bond, O, -O-C₁₋₂alkyl-, -CO-C₁₋₂alkyl-, -NR¹⁸-C₁₋₂alkyl-, -CO-NR¹⁹-, Het²⁴-C₁₋₂alkyl- or C₁₋₂alkyl;
- R¹ represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het¹ or C₁₋₄alkyloxy-;
- 35 R² represents hydrogen or halo;
- R³ represents hydrogen or cyano;
- R⁴ represents hydrogen or halo;

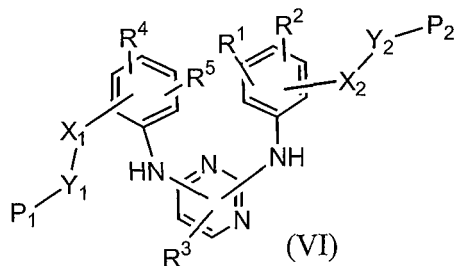
- R⁵ represents hydrogen, halo, C₁₋₆alkyloxy- or C₁₋₆alkyloxy- substituted with Het² or C₁₋₄alkyloxy-;
- R⁶ represents hydrogen;
- R⁷ represents hydrogen;
- 5 R¹¹ represents hydrogen or C₁₋₄alkyl;
- R¹³ represents hydrogen;
- R¹⁶ and R¹⁸ represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl-; in particular R¹⁶ and R¹⁸ represent hydrogen;
- R¹⁷ and R¹⁹ represent hydrogen;
- 10 L¹ represents C₁₋₈alkyl optionally substituted with one or where possible two or more substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;
- L² represents C₁₋₈alkyl optionally substituted with one or where possible two or more substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;
- 15 L³ represents C₁₋₈alkyl optionally substituted with one or where possible two or more substituents selected from phenyl, methylsulfide, cyano, polyhaloC₁₋₄alkyl-phenyl-, C₁₋₄alkyloxy, pyridinyl, mono- or di(C₁₋₄alkyl)-amino- or C₃₋₆cycloalkyl;
- Het¹ represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl;
- 20 Het² represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl;
- Het³ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl;
- Het⁴ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl;
- Het⁵ represents morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl;
- Het¹⁰ represents piperazinyl, piperidinyl, pyrrolidinyl or azetidiny;
- 25 Het¹⁷ represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl;
- Het²² represents morpholinyl, oxazolyl, isoxazolyl or piperazinyl wherein said Het²² is optionally substituted with C₁₋₄alkyl;
- Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²³ or Het²⁴ are optionally substituted with Het²²-carbonyl;
- 30 Het³² and Het³³ each independently represent a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl.

18. A compound according to any one of claims 16 to 17 for use as a medicine.

19. Use of a compound according to any one of claims 16 to 17 in the manufacture of a medicament for treating hyper proliferative disorders such as atherosclerosis, restenosis and cancer.
20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective kinase inhibitory amount of a compound as described in any one of the claims 16 to 17.
21. A process for preparing a compound as claimed in claims 1 to 6, comprising
- a) aminating in a first step a 2,4 or 4,6-di-I or di-Cl-pyrimidine (II) with an appropriate aniline of formula (III) to yield the anilinopyrimidine of general formula (IV),
 - b) further substituting said anilinopyrimidine with a further aniline of general formula (V) to provide the bis(aniline)pyrimidines of formula (VI), and
 - c) deprotection and ring closure provides the compounds of the present invention.



22. An intermediates of formula (VI)



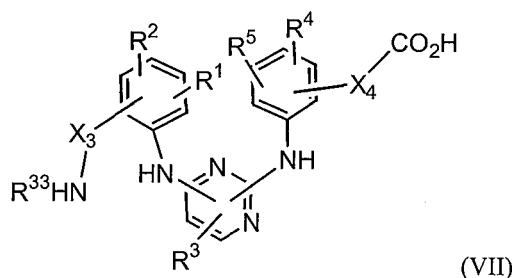
the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

P₁ and P₂ each independently represent hydroxy, halo, hydroxycarbonyl-, halocarbonyl-, amino or -NHR²⁹;

- 5 Y₁ and Y₂ each independently represent C₁₋₇alkyl, C₃₋₇alkenyl, Het²⁷, Het²⁸-CO, Het²⁹-C₁₋₅alkyl, L²-NH, L¹-NH-CO, L³-CO, L³-CO-NH, CO-C₁₋₆alkyl, NH-CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂, or CH₂-CO-NH-C₁₋₃alkyl; in particular Y₁ and Y₂ each independently represent C₁₋₇alkyl, C₃₋₇alkenyl, Het²⁷, Het²⁸-CO, L¹-NH, CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂ or CH₂-CO-NH-C₁₋₃alkyl; in a more
10 particular embodiment Y₁ and Y₂ each independently represent Het²⁷, Het²⁸-CO, L¹-NH, CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂ or CH₂-CO-NH-C₁₋₃alkyl;
- X¹ represents a direct bond, O, -O-C₁₋₂alkyl, CO, CO-C₁₋₂alkyl, NR¹⁶-C₁₋₂alkyl, CO-NR¹⁷, Het²³-C₁₋₂alkyl, or C₁₋₂alkyl;
- X² represents a direct bond, O, -O-C₁₋₂alkyl, CO, CO-C₁₋₂alkyl, NR¹⁸-C₁₋₂alkyl,
15 CO-NR¹⁶, Het²⁴-C₁₋₂alkyl, or C₁₋₂alkyl;
- R¹ represents hydrogen, halo, C₁₋₆alkyloxy or C₁₋₆alkyloxy substituted with Het¹ or C₁₋₄alkyloxy;
- R² represents hydrogen or halo;
- R³ represents hydrogen or cyano;
- 20 R⁴ represents hydrogen or halo;
- R⁵ represents hydrogen, halo, C₁₋₆alkyloxy or C₁₋₆alkyloxy substituted with Het² or C₁₋₄alkyloxy;
- R¹¹ represents hydrogen or C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl;
- R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl;
- 25 R¹⁷ and R¹⁹ each independently represent hydrogen;
- L¹ represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, mono- or di(C₁₋₄alkyl)amino, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl, imidazolyl or C₃₋₆cycloalkyl; in particular L¹ represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or
30 di(C₁₋₄alkyl)-amine or imidazolyl
- L² represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, mono- or di(C₁₋₄alkyl)amino, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl, imidazolyl or C₃₋₆cycloalkyl;
- L³ represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, mono- or
35 di(C₁₋₄alkyl)amino, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl, imidazolyl or C₃₋₆cycloalkyl;

- Het¹ represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het¹ represents morpholinyl or piperazinyl; more in particular Het¹ represents morpholinyl;
- Het² represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl; in particular Het² represents morpholinyl or piperazinyl; more in particular Het² represents morpholinyl;
- Het²² represents a heterocycle selected from morpholinyl, piperazinyl or piperidinyl wherein said Het²² is optionally substituted with C₁₋₄alkyl;
- Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl, piperazinyl or piperidinyl, wherein said Het²³ and Het²⁴ is optionally substituted with Het²²-carbonyl;
- Het²⁷ and Het²⁹ each independently represent a heterocycle selected from morpholinyl, pyrrolidinyl, --pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²⁷ and Het²⁹ are optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²²-carbonyl-, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-; in particular Het²⁷ and Het²⁹ are each independently selected from morpholinyl, piperazinyl or pyrrolidinyl; more in particular Het²⁷ and Het²⁹ are each independently selected from piperazinyl or pyrrolidinyl;
- Het²⁸ represents a heterocycle selected from morpholinyl, pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het²⁸ is optionally substituted with one or where possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-; in particular Het²⁸ is selected from morpholinyl, piperazinyl or pyrrolidinyl; more in particular Het²⁷ and Het²⁹ is selected from piperazinyl or pyrrolidinyl.

23. An intermediate of formula (VII)



- the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

- X₃ and X₄ each independently represent a direct bond, C₁₋₇alkyl, C₃₋₇alkenyl, C₃₋₇alkynyl, wherein said C₁₋₇alkyl, C₃₋₇alkenyl, C₃₋₇alkynyl are optionally substituted with one or where possible two or more substituents selected from amino, mono- or di(C₁₋₄alkyl)amino, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfonyl and C₁₋₄alkyloxycarbonylamino;
- 5 or X₃ and X₄ each independently represent C₁₋₅alkyl-O-C₁₋₅alkyl, C₁₋₅alkyl-NR³⁰-C₁₋₅alkyl, C₁₋₂alkyl-CO-Het¹⁰, Het²³, CR⁸R⁹ or O-C₁₋₂alkyl with the oxygen atom attached to the phenyl ring;
- 10 R¹ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-, halo-phenyl-carbonylamino-, Het²⁰, C₁₋₆alkoxy- substituted with halo, Het¹ or C₁₋₄alkyloxy-, or R¹ represents C₁₋₆alkyl substituted with one or where possible two or more substituents selected from hydroxy, Het¹⁸ or halo;
- 15 R² represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- 20 R³ represents hydrogen, cyano, nitro, C₁₋₄alkyl, or C₁₋₄alkyl substituted with one or more substituents selected from halo, C₁₋₄alkyloxy-, amino-, mono-or di(C₁₋₄alkyl)amino-, C₁₋₄alkyl-sulfonyl- or phenyl;
- R⁴ represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C₁₋₄alkyloxycarbonyl-, C₁₋₄alkylcarbonyl-, aminocarbonyl-, mono-or di(C₁₋₄alkyl)aminocarbonyl-, C₁₋₄alkyl-, C₂₋₆alkynyl-, C₃₋₆cycloalkyloxy-, aminosulfonyl, mono-or di(C₁₋₄alkyl)aminosulfonyl, C₁₋₄alkylsulfide, C₁₋₄alkylsulfoxide, C₁₋₄alkylsulfide or C₁₋₆alkoxy-;
- 25 R⁵ represents hydrogen, cyano, halo, hydroxy, formyl, C₁₋₆alkoxy-, C₁₋₆alkyl-, halo-phenyl-carbonylamino-, Het²¹, C₁₋₆alkoxy- substituted with halo, Het² or C₁₋₄alkyloxy-, or R⁵ represents C₁₋₆alkyl substituted with one or where possible two or more substituents selected from hydroxy, Het¹⁹ or halo;
- 30 R⁸ and R⁹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, indolyl, methylsulfide, hydroxy, thiol, hydroxyphenyl, C₁₋₄alkyloxyphenyl-, aminocarbonyl, hydroxycarbonyl, amino, mono- or di(C₁₋₄alkyl)-amine-, imidazolyl, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl, C₃₋₆cycloalkyl or guanidino;
- 35

- R³⁰ represents hydrogen, C₁₋₄alkyl, Het¹¹, Het¹²-C₁₋₄alkyl, phenyl-C₁₋₄alkyl, phenyl or mono- or di(C₁₋₄alkyl)amino-C₁₋₄alkyl-carbonyl wherein said R³⁰ is optionally substituted with hydroxy, amino, mono- or di(C₁₋₄alkyl)amino, pyrimidinyl or C₁₋₄alkyloxy;
- 5 R³³ represents hydrogen, C₁₋₄alkyl, Het¹⁴ or C₁₋₄alkyl substituted with one or where possible two or more substituents selected from hydroxy, amino, mono- or di(C₁₋₄alkyl)amino, phenyl, Het¹⁵ or C₁₋₂alkyloxy;
- Het¹ represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹ is optionally substituted
10 with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- Het² represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het² is optionally substituted
15 with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;
- Het¹⁰ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het¹⁰ is optionally substituted with one or where
20 possible two or more substituents selected from hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
- Het¹¹ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said Het¹¹ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
25
- Het¹² represent a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- 30 Het¹⁴ represent a heterocycle selected from pyrrolidinyl or piperidinyl wherein said pyrrolidinyl or piperazinyl are optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;
- Het¹⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het¹⁵ is optionally substituted with one or where possible
35 two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het¹⁸ and Het¹⁹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het¹⁸ or Het¹⁹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;

Het²⁰ and Het²¹ each independently represents a heterocycle selected from piperidinyl, morpholinyl, piperazinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het²⁰ or Het²¹ is optionally substituted with amino, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl-, phenyl, phenyl-C₁₋₄alkyl-, C₁₋₄alkyl-oxy-C₁₋₄alkyl- mono- or di(C₁₋₄alkyl)amino- or amino-carbonyl-;

Het²² represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

Het²³ represents a heterocycle selected from pyrrolidinyl, 2-pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl, piperazinyl or piperidinyl wherein said Het²³ is optionally substituted with one or where possible two or more substituents selected from hydroxy, Het²⁵, Het²²-carbonyl, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-; and

Het²⁵ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het²⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-;

provided said intermediate of formula (VII) is other than

2-[[2-[(3-aminophenyl)amino]-4-pyrimidinyl]amino]-Benzoic acid.

24. The intermediates according to claims 23 wherein;

P₁ and P₂ each independently represent hydroxy, halo, hydroxycarbonyl-, halocarbonyl-, amino or -NHR²⁹;

Y₁ and Y₂ each independently represent C₁₋₇alkyl, C₃₋₇alkenyl, Het²⁷, Het²⁸-CO, L¹-NH, CO-C₁₋₃alkyl, C₁₋₃alkyl-NR¹¹-CH₂ or CH₂-CO-NH-C₁₋₃alkyl;

X² represents a direct bond, O, -O-C₁₋₂alkyl, CO, CO-C₁₋₂alkyl, NR¹⁸-C₁₋₂alkyl, CO-NR¹⁶, Het²⁴-C₁₋₂alkyl, or C₁₋₂alkyl;

R¹ represents hydrogen, halo, C₁₋₆alkyloxy or C₁₋₆alkyloxy substituted with Het¹ or C₁₋₄alkyloxy;

- R² represents hydrogen or halo;
R³ represents hydrogen or cyano;
R⁴ represents hydrogen or halo;
R⁵ represents hydrogen, halo, C₁₋₆alkyloxy or C₁₋₆alkyloxy substituted with Het² or
5 C₁₋₄alkyloxy;
R¹¹ represents hydrogen or C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl;
R¹⁶ and R¹⁸ each independently represent hydrogen, C₁₋₄alkyl or Het¹⁷-C₁₋₄alkyl;
R¹⁷ and R¹⁹ each independently represent hydrogen;
L¹ represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, mono-or
10 di(C₁₋₄alkyl)amino, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl,
imidazolyl or C₃₋₆cycloalkyl;
L² represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, mono-or
di(C₁₋₄alkyl)amino, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl,
imidazolyl or C₃₋₆cycloalkyl;
15 L³ represents C₁₋₈alkyl optionally substituted with phenyl, methylsulfide, mono-or
di(C₁₋₄alkyl)amino, cyano, polyhaloC₁₋₄alkylphenyl, C₁₋₄alkyloxy, pyridinyl,
imidazolyl or C₃₋₆cycloalkyl;
Het¹ represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl;
Het² represents morpholinyl, oxazolyl, isoxazolyl, or piperazinyl;
20 Het²² represents a heterocycle selected from morpholinyl, piperazinyl or piperidinyl
wherein said Het²² is optionally substituted with C₁₋₄alkyl;
Het²³ and Het²⁴ each independently represent a heterocycle selected from pyrrolidinyl,
piperazinyl or piperidinyl, wherein said Het²³ and Het²⁴ is optionally substituted
with Het²²-carbonyl;
25 Het²⁷ and Het²⁹ each independently represent a heterocycle selected from morpholinyl,
pyrrolidinyl, --pyrrolidinonyl, quinolinyl, isoquinolinyl, decahydroquinolinyl,
piperazinyl or piperidinyl wherein said Het²⁷ and Het²⁹ are optionally substituted
with one or where possible two or more substituents selected from hydroxy,
Het²²-carbonyl-, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-;
30 Het²⁸ represents a heterocycle selected from morpholinyl, pyrrolidinyl, 2-
pyrrolidinonyl, piperazinyl or piperidinyl wherein said Het²⁸ is optionally
substituted with one or where possible two or more substituents selected from
hydroxy, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl- or polyhydroxy-C₁₋₄alkyl-.
- 35 25. The intermediates according to claims 23 wherein;

X₃ and X₄ each independently represent a direct bond, C₁₋₇alkyl, C₃₋₇alkenyl, C₁₋₅alkyl-NR³⁰-C₁₋₅alkyl, Het²³, CR⁸R⁹ or O-C₁₋₂alkyl with the oxygen atom attached to the phenyl ring;

R¹ represents hydrogen, halo, C₁₋₆alkyloxy-, or C₁₋₆alkyloxy substituted with Het¹ or C₁₋₄alkyloxy;

R² represents hydrogen or halo;

R³ represents hydrogen, cyano or nitro; in particular hydrogen or cyano;

R⁴ represents hydrogen or halo;

R⁵ represents hydrogen, halo, C₁₋₆alkyloxy-, or C₁₋₆alkyloxy substituted with Het² or C₁₋₄alkyloxy;

R⁸ and R⁹ each independently represents hydrogen or C₁₋₄alkyl optionally substituted with phenyl, methylsulfide, hydroxy, thiol, amino, mono- or di(C₁₋₄alkyl)-amine-, or imidazolyl;

R³⁰ represents hydrogen, C₁₋₄alkyl or Het¹²-C₁₋₄alkyl;

R³³ represents hydrogen, C₁₋₄alkyl or Het¹⁵-C₁₋₄alkyl;

Het¹ represents morpholinyl;

Het² represents morpholinyl;

Het¹² represents pyrrolidinyl or piperazinyl wherein said Het¹² is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-; in particular Het¹² represents pyrrolidinyl or piperazinyl;

Het¹⁵ represents pyrrolidinyl or piperazinyl wherein said Het¹⁵ is optionally substituted with one or where possible two or more substituents selected from C₁₋₄alkyl, C₃₋₆cycloalkyl, hydroxy-C₁₋₄alkyl-, C₁₋₄alkyloxyC₁₋₄alkyl or polyhydroxy-C₁₋₄alkyl-; in particular Het¹⁵ represents pyrrolidinyl or piperazinyl; and

Het²³ represents a heterocycle selected from pyrrolidinyl, decahydroquinolinyl or pyridinyl wherein said Het²³ is optionally substituted with one or where possible two or more substituents selected from hydroxy or C₁₋₄alkyl.

26. Use of an intermediate according to any one of claims 22 to 25 in the synthesis of a compound of formula (I).