MTKI QUINAZOLINE 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 their 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.

It is an object of the present invention to provide such kinase inhibitors, that are quinazoline derived macrocycles, hereinafter also referred to as multi targeting kinase inhibitors (MTKI), found to possess anti-proliferative activity, such as anti-cancer activity and which 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 quinazoline derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of anti-proliferative effect .

In particular, the compounds of the present invention were found to inhibit tyrosine kinase enzymes, also called tyrosine kinases. Tyrosine kinases are a class of enzymes, which catalyse the transfer of the terminal phosphate of adenosine triphosphate to the phenolic hydroxy- group of a tyrosine residue present in the target protein. It is known, that several oncogenes, involved in the transformation of a cell into a malignant tumour cell, encode tyrosine kinase enzymes including certain growth factor receptors such as EGF, FGF, IGF-1R, IR, PDGF and VEGF. This family of receptor tyrosine kinases and in particular the EGF family of receptor tyrosine kinases are frequently present in common human cancers such as breast cancer, non-small cell lung cancers including adenocarcinomas and squamous cell cancer of the lung, bladder cancer, ocsophageal cancer, gastrointestinal cancer such as colon, rectal or stomach cancer, cancer of the prostate, leukaemia and ovarian, bronchial or pancreatic cancer, which are examples of cell proliferation disorders.

Accordingly, it has been recognised that the selective inhibition of tyrosine kinases will be of value in the treatment of cell proliferation related disorders. Support for this view is provided by the development of Herceptin® (Trastuzumab) and Gleevec™ (imatinib mesylate) the first examples of target based cancer drugs. 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).

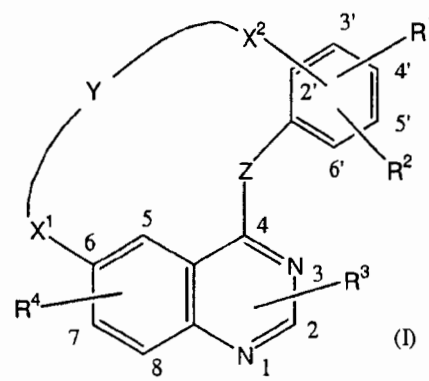
Further support is given by the demonstration that EGF receptor tyrosine kinase inhibitors, specifically attenuates the growth in athymic nude mice of transplanted carcinomas such as human mammary carcinoma or human squamous cell carcinoma (Review by T.R. Burke Jr., Drugs of the Future, 1992, 17, 119). As a consequence, to treat different cancers there has been considerable interest in the development of drugs that target the EGFR receptor. For example, several antibodies that bind to the extra-cellular domain of EGFR are undergoing clinical trials, including Erbitux™ (also called C225, Cetuximab), which was developed by Imclone Systems and is in Phase III clinical trials for the treatment of several cancers. Also, several promising orally active drugs that are potent and relatively specific inhibitors of the EGFR tyrosine kinase are now well advanced in clinical trials. The AstraZeneca compound ZD1839, which is now called IRESSA® and approved for the treatment of advanced non-small-cell lung cancer, and the OSI/Genentech/Roche compound OSI-774, which is now called Tarceva™ (erlotinib) , have shown marked efficacy against several cancers in human clinical trials (Morin M.J., "From oncogene to drug: development of small molecule tyrosine kinase inhibitors as anti-tumour and anti-angiogenic agents, 2000, Oncogene 19, 6574).

In addition to the above, EGF receptor tyrosine kinases are 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 disclosed in International Patent Application WO96/33980 and in J. Med. Chem, 2002, 45, 3865 that certain 4 anilino substituted quinazoline derivatives may be useful as inhibitors of tyrosine kinase and in particular of the EGF type receptor tyrosine kinases. Unexpectedly it was found that Quinazoline derivatives of the present formula (I) that are different in structure show to have tyrosine kinase inhibitory activity.

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

This invention concerns compounds of formula (I)



(I)

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

Z represents NH;

Y represents $-C_{3-9}$alkyl-, $-C_{2-9}$alkenyl-, $-C_{1-5}$alkyl-oxy-C_{1-5}alkyl-, $-C_{1-5}$alkyl-NR^{13}-C_{1-5}alkyl-, $-C_{1-5}$alkyl-NR^{14}-CO-C_{1-5}alkyl-, $-C_{1-6}$alkyl-NH-CO-, -NH-CO-C_{1-6}alkyl-, -CO-C_{1-7}alkyl-, $-C_{1-7}$alkyl-CO-, C_{1-6}alkyl-CO-C_{1-6}alkyl, $-C_{1-2}$alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-, $-C_{1-2}$alkyl-CO-NH-$CR^{18}R^{19}$-CO-, $-C_{1-2}$alkyl-CO-NR^{20}-C_{1-3}alkyl-CO-, $-C_{1-2}$alkyl-NR^{21}-CH_2-CO-NH-C_{1-3}alkyl-,

-NR^{22}-CO-C_{1-3}alkyl-NH-, -C_{1-3}alkyl-NH-CO-Het^{20}-, C_{1-2}alkyl-CO-Het^{21}-CO-, or -Het^{22}-CH_2-CO-NH-C_{1-3}alkyl-;

X^1 represents O, -O-C_{1-2}alkyl-, -O-N=CH-, NR^{11} or -NR^{11}-C_{1-2}alkyl-; in a particular embodiment X^1 represents O, -O-C_{1-2}alkyl- or NR^{11}-C_{1-2}alkyl;

X^2 represents a direct bond, C_{1-2}alkyl, O, -O-C_{1-2}alkyl-, CO, -CO-C_{1-2}alkyl-, -O-N=CH-, NR^{12} or NR^{12}-C_{1-2}alkyl-; in a particular embodiment X^2 represents a direct bond, -O-, -O-C_{1-2}alkyl, -CO-C_{1-2}alkyl- or NR^{12}-C_{1-2}alkyl-;

R^1 represents hydrogen, cyano, halo or hydroxy, preferably halo;

R^2 represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C_{1-4}alkyloxycarbonyl-, Het^{16}-carbonyl-, C_{1-4}alkyl-, C_{2-6}alkynyl-, Ar^5, Het^1 or dihydroxyborane;

R^3 represents hydrogen, cyano, halo, hydroxy, formyl, C_{1-6}alkoxy-, C_{1-6}alkyl-, C_{1-6}alkoxy- substituted with halo, or R^3 represents C_{1-4}alkyl substituted with one or where possible two or more substituents selected from hydroxy or halo;

R^4 represents Ar^4-C_{1-4}alkyloxy-, C_{1-4}alkyloxy- or R^4 represents C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from hydroxy-, halo, C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy-, $NR^{37}R^{38}$-carbonyloxy-, Het^5-carbonyloxy-, NR^7R^8, NR^9R^{10}-carbonyl-, Het^3-carbonyl-, Het^{13}-oxy- or Het^2-;

R^7 represents hydrogen, hydroxy-C_{1-4}alkyl- or C_{1-4}alkyl;

R^8 represents C_{3-6}cycloalkyl; Het^6-carbonyl-; Het^7-aminocarbonyl-; Het^8; Het^9-oxycarbonyl-; Het^{10}-sulfonyl-; C_{1-4}alkyloxycarbonyl; mono- or di(C_{1-4}alkyl)aminocarbonyl-; mono- or di(C_{1-4}alkyl)aminocarbonyl substituted with C_{1-4}alkylsulfonyl-; or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from C_{1-4}alkylsulfonyl, hydroxy- and C_{1-4}alkyloxy-; or

R^8 represents C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, $NR^{25}R^{26}$, aminocarbonyloxy-, C_{1-4}alkylcarbonyloxy-, aminocarbonyl-, hydroxy-C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy-, and Het^{11};

R^9 represents hydrogen or C_{1-4}alkyl-;

R^{10} represents Het^4 or C_{1-4}alkyl- substituted with C_{1-4}alkylsulfonyl-, ;

R^{11} represents hydrogen, C_{1-4}alkyl- or C_{1-4}alkyl-oxy-carbonyl-;

R^{12} represents hydrogen, C_{1-4}alkyl-, C_{1-6}alkyloxycarbonyl- or C_{1-6}alkyloxycarbonyl- substituted with phenyl;

R^{13} represents hydrogen, Het^{14}-C_{1-4}alkyl, C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl; in particular morpholinyl-C_{1-4}alkyl;

R^{14} and R^{15} are each independently selected from hydrogen, C_{1-4}alkyl, Het^{15}-C_{1-4}alkyl- or C_{1-4}alkyloxyC_{1-4}alkyl-;

R^{16} and R^{17} each independently represents hydrogen, C_{1-4}alkyl or C_{1-4}alkyl substituted with hydroxy-, C_{3-6}cycloalkyl or phenyl; or R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{18} represents hydrogen or C_{1-4}alkyl optionally substituted with hydroxy or phenyl;

R^{19} represents hydrogen or C_{1-4}alkyl, in particular hydrogen or methyl, even more particular hydrogen;

R^{20} represents hydrogen or C_{1-4}alkyl, in particular hydrogen or methyl;

R^{21} represents hydrogen, C_{1-4}alkyl, Het^{23}-C_{1-4}alkylcarbonyl- or R^{21} represents mono-or di(C_{1-4}alkyl)amino-C_{1-4}alkyl-carbonyl- optionally substituted with hydroxy, pyrimidinyl, dimethylamine or C_{1-4}alkyloxy;

R^{22} represents hydrogen or C_{1-4}alkyl optionally substituted with hydroxy or C_{1-4}alkyloxy;

R^{23} represents C_{1-4}alkyl optionally substituted with hydroxy-, C_{1-4}alkyloxy- or Het^{25}; R^{23} may also represent hydrogen when R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{25} and R^{26} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-, in particular R^{25} and R^{26} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl- or C_{1-4}alkylcarbonyl-;

R^{27} and R^{28} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-; or for those compounds of formula (I) wherein Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl or thiomorpholinyl substituted with $NR^{27}R^{28}$-C_{1-4}alkyl said R^{27} and R^{28} each independently represent C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{29} and R^{30} each independently represent hydrogen, aminosulfonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{31}R^{32}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-,

aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

R^{31} and R^{32} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{33} represents hydrogen or C_{1-4}alkyl;

R^{34} represents C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{35} represents hydrogen or C_{1-4}alkyl;

R^{36} represents C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{37} and R^{38} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, Het^{12} or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{39} and R^{40} each independently represent aminosulfonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- substituted with one or more substituents selected from $NR^{31}R^{32}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

Het^1 represents thiazolyl or 2-bora-1,3-dioxolanyl wherein said Het^1 is optionally substituted with one or where possible two, three, four or more substituents selected from 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-;

Het^2 represents a heterocycle selected from tetrahydropyranyl, tetrahydrofuranyl, furanyl, 1,1-dioxothiomorpholinyl, piperazininonyl, tetrahydro-1,1-dioxido-2H-

thiopyranyl, piperidinonyl, azetidinyl or 2-azetidinonyl wherein said Het^2 is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino, $NR^{29}R^{30}$, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{1-4}alkylsulfonyl or
C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or
C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-, or
C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or
C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or

Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, thiomorpholinyl or 1,1-dioxothiomorpholinyl wherein said Het^2 is optionally substituted with one or where possible two or more substituents selected from
C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or
C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-, or
C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or
C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

Het^3 represents a heterocycle selected from tetrahydropyranyl, tetrahydrofuranyl, furanyl, 1,1-dioxothiomorpholinyl, piperazininonyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, azetidinyl or 2-azetidinonyl wherein said Het^3 is optionally substituted with one or where possible two or more substituents hydroxy-, amino, C_{1-4}alkyl-, C_{3-6}cycloalkyl-C_{1-4}alkyl-, aminosulfonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, amino-C_{1-4}alkyl-, Mono- or di(C_{1-4}alkyl)amino-C_{1-4}alkyl, $NR^{35}R^{36}$, C_{1-4}alkyl-sulfonyl-C_{1-4}alkyl- or C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy- or hydroxy; or

Het^3 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, furanyl or pyrrolidinyl wherein said Het^3 is substituted with one or where possible two or more substituents selected from $NR^{35}R^{36}$, C_{1-4}alkyl-sulfonyl-C_{1-4}alkyl- or C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy- or hydroxy;

Het^4 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het^4 is substituted with one or where possible two or more substituents selected from C_{1-4}alkyl-sulfonyl-, C_{1-4}alkyl-, C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy- or hydroxy;

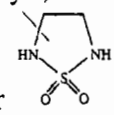
Het^5 represents a heterocycle selected from furanyl, piperazinyl, 1,1-dioxothiomorpholinyl, piperazininonyl, piperidinyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, morpholinyl or pyrrolidinyl wherein said Het^5 is optionally substituted with hydroxy, amino, mono- or di(C_{1-4}alkyl)-amino-, C_{1-4}alkyl,

Het^6 and Het^7 each independently represents a heterocycle selected from piperazinyl, piperidinyl or pyrrolidinyl wherein said heterocycles are optionally substituted with one or more substituents selected from hydroxy-, amino, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxy-C_{1-4}alkyl- and C_{1-4}alkyl-;

Het^8 represents a heterocycle selected from tetrahydropyranyl, tetrahydrofuranyl, 1,1-dioxothiomorpholinyl, piperazininonyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, azetidinyl or 2-azetidinonyl wherein said Het^8 is optionally substituted with aminosulfonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- optionally substituted with one or more substituents selected from amino, mono- or di(C_{1-4}alkyl)amino-, $NR^{33}R^{34}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or

Het^8 represents a heterocycle selected from furanyl, piperidinyl or piperazinyl wherein said Het^8 is substituted with aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- substituted with one or more substituents selected from $NR^{33}R^{34}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

Het^9 and Het^{10} each independently represents a heterocycle selected from piperazinyl, piperidinyl or pyrrolidinyl wherein said heterocycles are optionally substituted with one or more substituents selected from hydroxy-, amino, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxy-C_{1-4}alkyl- and C_{1-4}alkyl-;

Het^{11} represents 2-imidazolidinonyl- or ;

Het^{12} represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^{12} is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino or C_{1-4}alkyl-;

Het^{13} represents a heterocycle selected from furanyl, piperazinyl, 1,1-dioxothiomorpholinyl, piperazininonyl, piperidinyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, morpholinyl, piperazinyl or pyrrolidinyl;

Het^{14} and Het^{15} each independently represent a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^{14} and Het^{15} are optionally substituted with one or where possible two or more substituents selected from hydroxy, amino or C_{1-4}alkyl;

Het^{16} represents a heterocycle selected from piperidinyl or pyrrolidinyl;

Het^{20} represents pyrrolidinyl, 2-pyrrolidinonyl, piperidinyl or hydroxy-pyrrolidinyl, preferably pyrrolidinyl or hydroxy-pyrrolidinyl;

Het^{21} represents pyrrolidinyl or hydroxy-pyrrolidinyl;

Het^{22} represents pyrrolidinyl, piperazinyl or piperidinyl;

Het^{23} and Het^{25} each independently represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het^{23} is optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-;

Het^{24} represents morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl;

Ar^4, Ar^5 or Ar^6 each independently represent phenyl optionally substituted with nitro, cyano, C_{1-4}alkylsulfonyl-, C_{1-4}alkylsulfonylamino-, aminosulfonylamino-, hydroxy-C_{1-4}alkyl, aminosulfonyl-, hydroxy-, C_{1-4}alkyloxy- or C_{1-4}alkyl, preferably Ar^4 or Ar^5 each independently represent phenyl optionally substituted with cyano;

further characterised in that either

Y represents -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-;

Het^1 represents 2-bora-1,3-dioxolanyl optionally substituted with one or where possible two, three, four or more substituents selected from 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-;

R^{13} represents C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl; or

R^4 represents C_{1-4}alkyloxy substituted with at least one substituent selected from C_{1-4}alkyloxy-C_{1-4}alkyloxy-, $NR^{37}R^{38}$-carbonyloxy-, Het^5-carbonyloxy-, NR^7R^8, NR^9R^{10}-carbonyl-, Het^3-carbonyl-, Het^{13}-oxy- or Het^2-; wherein

R^8 represents Het^7-aminocarbonyl-; Het^9-oxycarbonyl-; Het^{10}-sulfonyl-; C_{1-4}alkyloxycarbonyl; mono- or di(C_{1-4}alkyl)aminocarbonyl-; mono- or di(C_{1-4}alkyl)aminocarbonyl substituted with C_{1-4}alkylsulfonyl-; or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from C_{1-4}alkylsulfonyl, hydroxy- and C_{1-4}alkyloxy-; or

R^8 represents C_{1-4}alkyl substituted with one or more substituents selected from hydroxy C_{1-4}alkylsulfonyl-, $NR^{25}R^{26}$, aminocarbonyloxy-, C_{1-4}alkylcarbonyloxy-, aminocarbonyl-, C_{1-4}alkyloxy-C_{1-4}alkyloxy-, and Het^{11};

Het^{13} represents C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl; in particular morpholinyl-C_{1-4}alkyl; and

Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl or thiomorpholinyl said Het^2 substituted with one or where possible two or more substituents selected from C_{1-4}alkyl- substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-; or

C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-; or

C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

or Het^2 represents 1,1-dioxothiomorpholinyl optionally substituted with C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-; or

C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-; or

C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-.

As used in the foregoing definitions and hereinafter,

- halo is generic to fluoro, chloro, bromo and iodo;
- C_{1-2}alkyl defines methyl or ethyl;
- C_{1-3}alkyl 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;
- C_{1-4}alkyl 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;
- C_{1-5}alkyl 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;
- C_{1-6}alkyl is meant to include C_{1-5}alkyl and the higher homologues thereof having 6 carbon atoms such as, for example hexyl, 1,2-dimethylbutyl, 2-methylpentyl and the like;
- C_{1-7}alkyl is meant to include C_{1-6}alkyl and the higher homologues thereof having 7 carbon atoms such as, for example 1,2,3-dimethylbutyl, 1,2-methylpentyl and the like;
- C_{3-9}alkyl 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;
- C_{2-4}alkenyl 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;
- C_{3-9}alkenyl 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;
- C_{2-6}alkynyl 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;
- C_{3-6}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;
- C_{1-4}alkyloxy defines straight or branched saturated hydrocarbon radicals such as methoxy, ethoxy, propyloxy, butyloxy, 1-methylethyloxy, 2-methylpropyloxy and the like;

- C_{1-6}alkyloxy is meant to include C_{1-4}alkyloxy and the higher homologues such as methoxy, ethoxy, propyloxy, butyloxy, 1-methylethyloxy, 2-methylpropyloxy and the like;
- polyhydroxy-C_{1-4}alkyl is generic to a C_{1-4}alkyl as defined hereinbefore, having two, three or where 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 –CH(=O). When X^1 represents the divalent radical –O-N=CH-, said radical is attached with the carbon atom to the R^3, R^4 bearing cyclic moiety of the compounds of formula (I) and when X^2 represents the divalent radical –O-N=CH-, said radical is attached with the carbon atom to the R^1, R^2 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; pyranyl includes 2*H*-pyranyl and 4*H*-pyranyl.

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, 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.
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.

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

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.

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 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.

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.

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

Y represents -C_{3-9}alkyl-, -C_{2-9}alkenyl-, -C_{1-5}alkyl-oxy-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-6}alkyl-NH-CO-, -NH-CO-C_{1-6}alkyl-, -CO-C_{1-7}alkyl-, -C_{1-7}alkyl-CO-, C_{1-6}alkyl-CO-C_{1-6}alkyl, -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-, -C_{1-2}alkyl-CO-NH-$CR^{18}R^{19}$-CO-, -C_{1-2}alkyl-CO-NR^{20}-C_{1-3}alkyl-CO-, -C_{1-2}alkyl-NR^{21}-CH_2-CO-NH-C_{1-3}alkyl-, -NR^{22}-CO-C_{1-3}alkyl-NH-, -C_{1-3}alkyl-NH-CO-Het^{20}-, C_{1-2}alkyl-CO-Het^{21}-CO-, or -Het^{22}-CH_2-CO-NH-C_{1-3}alkyl-;

X^1 represents O, -O-C_{1-2}alkyl-, -O-N=CH-, NR^{11} or -NR^{11}-C_{1-2}alkyl-; in a particular embodiment X^1 represents O, -O-C_{1-2}alkyl- or NR^{11}-C_{1-2}alkyl;

X^2 represents a direct bond, C_{1-2}alkyl, O, -O-C_{1-2}alkyl-, CO, -CO-C_{1-2}alkyl-, -O-N=CH-, NR^{12} or NR^{12}-C_{1-2}alkyl-; in a particular embodiment X^2 represents a direct bond, -O-, -O-C_{1-2}alkyl, -CO-C_{1-2}alkyl- or NR^{12}-C_{1-2}alkyl-;

R^1 represents hydrogen, cyano, halo or hydroxy, preferably halo;

R^2 represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C_{1-4}alkyloxycarbonyl-, Het^{16}-carbonyl-, C_{1-4}alkyl-, C_{2-6}alkynyl-, Ar^5, Het^1 or dihydroxyborane;

R^3 represents hydrogen, cyano, halo, hydroxy, formyl, C_{1-6}alkoxy-, C_{1-6}alkyl-, C_{1-6}alkoxy- substituted with halo, or R^3 represents C_{1-4}alkyl substituted with one or where possible two or more substituents selected from hydroxy or halo;

R^4 represents Ar^4-C_{1-4}alkyloxy-, C_{1-4}alkyloxy- or R^4 represents C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from hydroxy-, halo, C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy-, $NR^{37}R^{38}$-carbonyloxy-, Het^5-carbonyloxy-, NR^7R^8, NR^9R^{10}-carbonyl-, Het^3-carbonyl-, Het^{13}-oxy- or Het^2-;

R^7 represents hydrogen or C_{1-4}alkyl;

R^8 represents C_{3-6}cycloalkyl, Het^6-carbonyl-, Het^7-aminocarbonyl-, Het^8, Het^9-oxycarbonyl-, Het^{10}-sulfonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl substituted with C_{1-4}alkylsulfonyl-, or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from C_{1-4}alkylsulfonyl, hydroxy- and C_{1-4}alkyloxy-, or R^8 represents C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, $NR^{25}R^{26}$, aminocarbonyloxy-, aminocarbonyl-, C_{1-4}alyloxy-C_{1-4}alkyloxy-, and Het^{11};

R^9 represents hydrogen or C_{1-4}alkyl-;

R^{10} represents Het^4 or C_{1-4}alkyl- substituted with C_{1-4}alkylsulfonyl-, ;

R^{11} represents hydrogen, C_{1-4}alkyl- or C_{1-4}alkyl-oxy-carbonyl-;

R^{12} represents hydrogen, C_{1-4}alkyl-, C_{1-6}alkyloxycarbonyl- or C_{1-6}alkyloxycarbonyl- substituted with phenyl;

R^{13} represents hydrogen, Het^{14}-C_{1-4}alkyl, C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl; in particular morpholinyl-C_{1-4}alkyl;

R^{14} and R^{15} are each independently selected from hydrogen, C_{1-4}alkyl, Het^{15}-C_{1-4}alkyl- or C_{1-4}alkyloxyC_{1-4}alkyl-;;

R^{16} and R^{17} each independently represents hydrogen, C_{1-4}alkyl or C_{1-4}alkyl substituted with hydroxy- or phenyl; or R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{18} represents hydrogen or C_{1-4}alkyl optionally substituted with hydroxy or phenyl;

R^{19} represents hydrogen or C_{1-4}alkyl, in particular hydrogen or methyl, even more particular hydrogen;

R^{20} represents hydrogen or C_{1-4}alkyl, in particular hydrogen or methyl;

R^{21} represents hydrogen, C_{1-4}alkyl, Het^{23}-C_{1-4}alkylcarbonyl- or R^{21} represents mono-or di(C_{1-4}alkyl)amino-C_{1-4}alkyl-carbonyl- optionally substituted with hydroxy, pyrimidinyl, dimethylamine or C_{1-4}alkyloxy;

R^{22} represents hydrogen or C_{1-4}alkyl optionally substituted with hydroxy or C_{1-4}alkyloxy;

R^{23} represents C_{1-4}alkyl optionally substituted with hydroxy-, C_{1-4}alkyloxy- or Het^{23}; R^{23} may also represent hydrogen when R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{25} and R^{26} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-, in particular R^{25} and R^{26} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl- or C_{1-4}alkylcarbonyl-;

R^{27} and R^{28} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{29} and R^{30} each independently represent hydrogen, aminosulfonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{31}R^{32}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or

C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

R^{31} and R^{32} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{33} represents hydrogen or C_{1-4}alkyl;

R^{34} represents C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{35} represents hydrogen or C_{1-4}alkyl;

R^{36} represents C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{37} and R^{38} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, Het^{12} or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{39} and R^{40} each independently represent aminosulfonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- substituted with one or more substituents selected from $NR^{31}R^{32}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

Het^1 represents thiazolyl or 2-bora-1,3-dioxolanyl wherein said Het^1 is optionally substituted with one or where possible two, three, four or more substituents selected from 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-;

Het^2 represents a heterocycle selected from tetrahydropyranyl, tetrahydrofuranyl, furanyl, 1,1-dioxothiomorpholinyl, piperazininonyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, azetidinyl or 2-azetidinonyl wherein said Het^2 is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino, $NR^{29}R^{30}$, aminocarbonyl, mono- or

di(C_{1-4}alkyl)aminocarbonyl, C_{1-4}alkylsulfonyl or
C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or
C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-, or
C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or
C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or

Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl are optionally substituted with one or where possible two or more substituents selected from
C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or
C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-, or
C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or
C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

Het^3 represents a heterocycle selected from tetrahydropyranyl, tetrahydrofuranyl, furanyl, 1,1-dioxothiomorpholinyl, piperazininonyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, azetidinyl or 2-azetidinonyl wherein said Het^3 is optionally substituted with one or where possible two or more substituents hydroxy-, amino, C_{1-4}alkyl-, C_{3-6}cycloalkyl-C_{1-4}alkyl-, aminosulfonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, amino-C_{1-4}alkyl-, Mono- or di(C_{1-4}alkyl)amino-C_{1-4}alkyl, $NR^{35}R^{36}$, C_{1-4}alkyl-sulfonyl-C_{1-4}alkyl- or C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy- or hydroxy; or

Het^3 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^3 is optionally substituted with one or where possible two or more substituents selected from $NR^{35}R^{36}$, C_{1-4}alkyl-sulfonyl-C_{1-4}alkyl- or C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy- or hydroxy;

Het^4 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het^4 is substituted with one or

where possible two or more substituents selected from C_{1-4}alkyl-sulfonyl-C_{1-4}alkyl-, C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy- or hydroxy;

Het^5 represents a heterocycle selected from furanyl, piperazinyl, 1,1-dioxothiomorpholinyl, piperazininonyl, piperidinyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, morpholinyl or pyrrolidinyl wherein said Het^5 is optionally substituted with hydroxy, amino, mono- or di(C_{1-4}alkyl)-amino-, C_{1-4}alkyl,

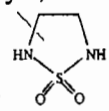
Het^6 and Het^7 each independently represents a heterocycle selected from piperazinyl, piperidinyl or pyrrolidinyl wherein said heterocycles are optionally substituted with one or more substituents selected from hydroxy-, amino-, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxy-C_{1-4}alkyl- and C_{1-4}alkyl-;

Het^8 represents a heterocycle selected from tetrahydropyranyl, tetrahydrofuranyl, 1,1-dioxothiomorpholinyl, piperazininonyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, azetidinyl or 2-azetidinonyl wherein said Het^8 is optionally substituted with aminosulfonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- optionally substituted with one or more substituents selected from amino, mono- or di(C_{1-4}alkyl)amino-, $NR^{33}R^{34}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or
C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or
C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or

Het^8 represents a heterocycle selected from furanyl, piperidinyl or piperazinyl wherein said Het^8 is substituted with aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- substituted with one or more substituents selected from $NR^{33}R^{34}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or
C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or
C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

Het^9 and Het^{10} each independently represents a heterocycle selected from piperazinyl, piperidinyl or pyrrolidinyl wherein said heterocycles are optionally substituted

with one or more substituents selected from hydroxy-, amino, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxy-C_{1-4}alkyl- and C_{1-4}alkyl-;

Het^{11} represents 2-imidazolidinonyl- or ;

Het^{12} represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^{12} is optionally substituted with one or where possible two or more substituents selected from hydroxy-, amino or C_{1-4}alkyl-;

Het^{13} represents a heterocycle selected from furanyl, piperazinyl, 1,1-dioxothiomorpholinyl, piperazininonyl, piperidinyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, morpholinyl, piperazinyl or pyrrolidinyl

Het^{16} represents a heterocycle selected from piperidinyl or pyrrolidinyl;

Het^{20} represents pyrrolidinyl, 2-pyrrolidinonyl, piperidinyl or hydroxy-pyrrolidinyl, preferably pyrrolidinyl or hydroxy-pyrrolidinyl;

Het^{21} represents pyrrolidinyl or hydroxy-pyrrolidinyl;

Het^{22} represents pyrrolidinyl, piperazinyl or piperidinyl;

Het^{23} represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het^{23} is optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-;

Ar^4, Ar^5 or Ar^6 each independently represent phenyl optionally substituted with nitro, cyano, C_{1-4}alkylsulfonyl-, C_{1-4}alkylsulfonylamino-, aminosulfonylamino-, hydroxy-C_{1-4}alkyl, aminosulfonyl-, hydroxy-, C_{1-4}alkyloxy- or C_{1-4}alkyl, preferably Ar^4 or Ar^5 each independently represent phenyl optionally substituted with cyano;

further characterised in that either

Y represents -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-;

Het^1 represents 2-bora-1,3-dioxolanyl optionally substituted with one or where possible two, three, four or more substituents selected from 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-;

R^{13} represents C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl; or

R^4 represents C_{1-4}alkyloxy substituted with at least one substituent selected from C_{1-4}alkyloxy-C_{1-4}alkyloxy-, $NR^{37}R^{38}$-carbonyloxy-, Het^5-carbonyloxy-, NR^7R^8, NR^9R^{10}-carbonyl-, Het^3-carbonyl-, Het^{13}-oxy- or Het^2-.

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;

Z represents NH;

Y represents -C_{3-9}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-6}alkyl-CO-NH-, -C_{1-6}alkyl-NH-CO-, -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-, -C_{1-2}alkyl-NR^{21}-CH_2-CO-NH-C_{1-3}alkyl or C_{1-3}alkyl-NH-CO-Het^{20}-; in particular Y represents -C_{3-9}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-6}alkyl-CO-NH-, -C_{1-6}alkyl-NH-CO-, -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH- or C_{1-3}alkyl-NH-CO-Het^{20}-

X^1 represents a direct bond, O, -O-C_{1-2}alkyl-, NR^{11}, or -NR^{11}-C_{1-2}alkyl-;

X^2 represents a direct bond, -C_{1-2}alkyl-, CO-C_{1-2}alkyl or NR^{12}-C_{1-2}alkyl-; in particular X^2 represents a direct bond, -C_{1-2}alkyl- or NR^{12}-C_{1-2}alkyl-;

R^1 represents hydrogen, cyano, halo or hydroxy;

R^2 represents hydrogen, halo, cyano, C_{2-6}alkynyl, hydroxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl- or Het^1; in particular R^2 represents hydrogen, halo, cyano, acetylene (-C≡CH), hydroxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl- or Het^1; more in particular R^2 represents hydrogen, halo, cyano, hydroxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl- or Het^1

R^3 represents hydrogen, cyano, halo, hydroxy, formyl, C_{1-6}alkyloxy or C_{1-6}alkyloxy- substituted with halo;

R^4 represents Ar^4-C_{1-4}alkyloxy, C_{1-4}alkyloxy-, or C_{1-4}alkyloxy- substituted with one or where possible two or more substituents selected from hydroxy, C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy, NR^7R^8 or Het^2; in particular R^4 represents Ar^4-C_{1-4}alkyloxy, C_{1-4}alkyloxy-, or C_{1-4}alkyloxy- substituted with one or where possible two or more substituents selected from C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy or NR^7R^8

R^7 represents hydrogen, hydroxyC_{1-4}alkyl- or C_{1-4}alkyl;

R^8 represents C_{1-4}alkyloxycarbonyl or C_{1-4}alkyl- substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, C_{1-4}alkylcarbonyloxy or $NR^{25}R^{26}$; in particular R^8 represents C_{1-4}alkyl- substituted with one or more substituents selected from C_{1-4}alkylsulfonyl- or $NR^{25}R^{26}$;

R^{11} represents hydrogen, C_{1-4}alkyloxycarbonyl or C_{1-4}alkyl; in particular R^{11} represents hydrogen or C_{1-4}alkyl;

R^{12} represents hydrogen or C_{1-4}alkyl;

R^{13} represents C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl;

R^{14} and R^{15} each independently represent hydrogen or C_{1-4}alkyl; in particular R^{14} and R^{15} each independently represent hydrogen;

R^{16} and R^{17} each independently represent hydrogen or C_{1-4}alkyl optionally substituted with C_{3-6}cycloalkyl or R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl; in a particular embodiment R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{21} represents hydrogen or C_{1-4}alkyloxycarbonyl; in particular R^{21} represents C_{1-4}alkyloxycarbonyl

R^{23} represents C_{1-4}alkyl optionally substituted with hydroxy-, C_{1-4}alkyloxy- or Het^{25}; R^{23} may also represent hydrogen when R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{25} and R^{26} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl, C_{1-4}alkyloxycarbonyl or C_{1-4}alkylcarbonyl; in particular R^{25} and R^{26} each independently represents hydrogen or C_{1-4}alkylcarbonyl;

R^{27} and R^{28} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl, C_{1-4}alkyloxycarbonyl or C_{1-4}alkylcarbonyl; in particular R^{27} and R^{28} each independently represent hydrogen or C_{1-4}alkylcarbonyl;

Het^1 represents 2-bora-1,3-dioxolanyl- optionally substituted with one or where possible two, three, four or more substituents selected from amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl-, mono- or di(C_{1-4}alkyl)amino- or aminocarbonyl-;

Het^2 represents 1,1-dioxothiomorpholinyl optionally substituted with C_{1-4}alkyloxycarbonyl or C_{1-4}alkyl-$NR^{27}R^{28}$; or Het^2 represents piperidinyl or piperazinyl substituted with C_{1-4}alkyloxycarbonyl or -C_{1-4}alkyl-$NR^{27}R^{28}$;

Het^{20} represents pyrrolidinyl, 2-pyrrolidinonyl, piperidinyl or hydroxy-pyrrolidinyl; in particular Het^{20} represents pyrrolidinyl, piperidinyl or hydroxy-pyrrolidinyl; more in particular Het^{20} represents pyrrolidinyl;

Het^{25} represents a heterocycle selected from morpholinyl or piperazinyl wherein said heterocycle is optionally substituted with C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyloxy-C_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl; or

Ar^4, Ar^5 or Ar^6 each independently represents phenyl optionally substituted with nitro, cyano, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkyl or C_{1-4}alkyloxy;

further characterised in that either

Y represents –C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-; or

R^4 represents C_{1-4}alkyloxy substituted with at least one substituent selected from C_{1-4}alkyloxy-C_{1-4}alkyloxy-, NR^7R^8 or Het^2.

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;

Z represents NH;

Y represents -C_{3-9}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-6}alkyl-CO-NH-, -C_{1-6}alkyl-NH-CO-, -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-, -C_{1-2}alkyl-NR^{21}-CH_2-CO-NH-C_{1-3}alkyl or C_{1-3}alkyl-NH-CO-Het^{20}-; in particular Y represents -C_{3-9}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-6}alkyl-CO-NH-, -C_{1-6}alkyl-NH-CO-, -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH- or C_{1-3}alkyl-NH-CO-Het^{20}-

X^1 represents a direct bond, O, -O-C_{1-2}alkyl-, NR^{11}, or -NR^{11}-C_{1-2}alkyl-;

X^2 represents a direct bond, -C_{1-2}alkyl-, CO-C_{1-2}alkyl or NR^{12}-C_{1-2}alkyl-; in particular X^2 represents a direct bond, -C_{1-2}alkyl- or NR^{12}-C_{1-2}alkyl-;

R^1 represents hydrogen or halo;

R^2 represents hydrogen, halo, C_{2-6}alkynyl, cyano or Het^1; in particular R^2 represents hydrogen, halo, C_{2-6}alkynyl or Het^1; more in particular R^2 represents hydrogen, halo, acetylene or Het^1; or R^2 represents hydrogen, halo, cyano or Het^1;

R^3 represents hydrogen;

R^4 represents Ar^4-C_{1-4}alkyloxy, C_{1-4}alkyloxy-, or C_{1-4}alkyloxy- substituted with one or where possible two or more substituents selected from hydroxy, C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy, NR^7R^8 or Het^2; in particular R^4 represents Ar^4-C_{1-4}alkyloxy, C_{1-4}alkyloxy-, or C_{1-4}alkyloxy- substituted with one or where possible two or more substituents selected from C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy or NR^7R^8

R^7 represents hydrogen or C_{1-4}alkyl;

R^8 represents C_{1-4}alkyloxycarbonyl or C_{1-4}alkyl- substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy, C_{1-4}alkylcarbonyloxy or $NR^{25}R^{26}$; in particular R^8 represents C_{1-4}alkyl- substituted with one or more substituents selected from C_{1-4}alkylsulfonyl- or $NR^{25}R^{26}$;

R^{11} represents hydrogen or C_{1-4}alkyl;

R^{12} represents hydrogen or C_{1-4}alkyl;

R^{13} represents Ar^6-sulfonyl or C_{1-6}alkyloxycarbonyl optionally substituted with phenyl;

R^{14} and R^{15} represent hydrogen;

R^{16} and R^{17} each independently represent hydrogen or C_{1-4}alkyl optionally substituted with C_{3-6}cycloalkyl or R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl; in a particular embodiment R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{21} represents hydrogen or C_{1-4}alkyloxycarbonyl;

R^{23} represents C_{1-4}alkyl optionally substituted with hydroxy-, C_{1-4}alkyloxy- or Het^{25}; R^{23} may also represent hydrogen when R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{25} and R^{26} each independently represent hydrogen or C_{1-4}alkylcarbonyl;

R^{27} and R^{28} each independently represent hydrogen or C_{1-4}alkylcarbonyl;

Het^1 represents 2-bora-1,3-dioxolanyl-;

Het^2 represents 1,1-dioxothiomorpholinyl, piperidinyl or piperazinyl wherein said Het^2 is optionally substituted with C_{1-4}alkyloxycarbonyl or -C_{1-4}alkyl-$NR^{27}R^{28}$;

Het^{20} represents pyrrolidinyl;

Het^{25} represents a heterocycle selected from morpholinyl or piperazinyl wherein said heterocycle is optionally substituted with C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyloxy-C_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl;

Ar^4 represents phenyl;

Ar^5 represents phenyl; or

Ar^6 represents phenyl optionally substituted with nitro;

further characterised in that either

Y represents –C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-; or

R^4 represents C_{1-4}alkyloxy substituted with at least one substituent selected from C_{1-4}alkyloxy-C_{1-4}alkyloxy-, NR^7R^8 or Het^2; in particular C_{1-4}alkyloxy substituted with C_{1-4}alkyloxy-C_{1-4}alkyloxy- or NR^7R^8.

An interesting group of compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

Z represents NH;

Y represents -C_{3-9}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-2}alkyl-NR^{21}-H_2-CO-NH-C_{1-3}alkyl- or –C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-; in particular Y represents -C_{3-9}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl- or –C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-

X^1 represents O or -O-C_{1-2}alkyl-; inparticular X^1 represents O

X^2 represents a direct bond, C_{1-2}alkyl, -CO-C_{1-2}alkyl or NR^{12}-C_{1-2}alkyl; in particular X^2 represents a direct bond or NR^{12}-C_{1-2}alkyl-;

R^1 represents hydrogen or halo; in particular R^1 represents hydrogen;

R^2 represents halo, C_{2-6}alkynyl, cyano or Het^1; in particular R^2 represents halo, acetylene or Het^1; more in particular R^2 represents halo or Het^1;

R^3 represents hydrogen;

R^4 represents Ar^4-C_{1-4}alkyloxy-, C_{1-4}alkyloxy- or C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from Het^2, NR^7R^8, hydroxy and C_{1-4}alkyloxy-C_{1-4}alkyloxy-; in particular R^4 represents Ar^4-C_{1-4}alkyloxy-, C_{1-4}alkyloxy- or C_{1-4}alkyloxy substituted with C_{1-4}alkyloxy-C_{1-4}alkyloxy-;

R^7 represents hydrogen or C_{1-4}alkyl;

R^8 represents C_{1-4}alkyl substituted with $NR^{25}R^{26}$ or C_{1-4}alkylsulfonyl;

R^{12} represents hydrogen or C_{1-4}alkyl-;

R^{13} represents Ar^6-sulfonyl or C_{1-6}alkyloxycarbonyl optionally substituted with phenyl;

R^{16} and R^{17} represents hydrogen, C_{1-4}alkyl or R^{16} and R^{17} taken together with the carbon atom to which they are attached from a C_{3-6}cycloalkyl;

R^{23} represents hydrogen or C_{1-4}alkyl; in particular R^{23} represents C_{1-4}alkyl and R^{23} represents hydrogen when R^{16} and R^{17} taken together with the carbon atom to which they are attached from a C_{3-6}cycloalkyl;

R^{25} and R^{26} each independently represent hydrogen or C_{1-4}alkylcarbonyl;

R^{27} and R^{28} each independently represent hydrogen or C_{1-4}alkylcarbonyl;

Het^1 represents 2-bora-1,3-dioxolanyl;

Het^2 represents piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or 1,1-dioxothiomorpholinyl wherein said Het^2 is optionally substituted with C_{1-4}alkyloxycarbonyl or $NR^{27}R^{28}$-C_{1-4}alkyl; in particular Het^2 represents 1,1-dioxothiomorpholinyl; piperidinyl substituted with C_{1-4}alkyloxycarbonyl; or piperazinyl substituted with C_{1-4}alkyloxycarbonyl or $NR^{27}R^{28}$-C_{1-4}alkyl-;

Ar^4 represents phenyl;

Ar^5 represents phenyl; or

Ar^6 represents phenyl optionally substituted with nitro.

An interesting group of compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

Z represents NH;

Y represents -C_{3-9}alkyl-,-C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-2}alkyl-NR^{21}-CH_2-CO-NH-C_{1-3}alkyl-, C_{1-6}alkyl-NH-CO- or –C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-; in particular Y represents -C_{3-9}alkyl-, C_{1-6}alkyl-NH-CO--C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, or –C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-

X^1 represents O or -O-C_{1-2}alkyl-; in particular X^1 represents O

X^2 represents a direct bond, C_{1-2}alkyl, -CO-C_{1-2}alkyl or NR^{12}-C_{1-2}alkyl; in particular X^2 represents -CO-C_{1-2}alkyl or NR^{12}-C_{1-2}alkyl-;

R^1 represents hydrogen, cyano or halo; in particular R^1 represents hydrogen or halo, more in particular R^1 represents hydrogen, fluoro or bromo;

R^2 represents halo, C_{2-6}alkynyl, cyano or Het^1; in particular R^2 represents halo, acetylene or Het^1; more in particular R^2 represents halo or Het^1;

R^3 represents hydrogen;

R^4 represents Ar^4-C_{1-4}alkyloxy-, C_{1-4}alkyloxy- or C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from Het^2, NR^7R^8, hydroxy and C_{1-4}alkyloxy-C_{1-4}alkyloxy-; in particular R^4 represents Ar^4-C_{1-4}alkyloxy-, C_{1-4}alkyloxy- or C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from Het^2, NR^7R^8 or hydroxy;

R^7 represents hydrogen, hydroxy-C_{1-4}alkyl- or C_{1-4}alkyl;

R^8 represents C_{1-4}alkylcarbonyl , C_{1-4}alkyloxycarbonyl or C_{1-4}alkyl substituted with hydroxy-C_{1-4}alkyloxy-, $NR^{25}R^{26}$, C_{1-4}alkylcarbonyloxy- or C_{1-4}alkylsulfonyl;

R^{12} represents hydrogen or C_{1-4}alkyl-;

R^{13} represents Ar^6-sulfonyl or C_{1-6}alkyloxycarbonyl optionally substituted with phenyl;

R^{16} and R^{17} each independently represents hydrogen, C_{1-4}alkyl or R^{16} and R^{17} taken together with the carbon atom to which they are attached from a C_{3-6}cycloalkyl;

R^{23} represents C_{1-4}alkyl optionally substituted with Het^{25};

R^{23} may also represent hydrogen when R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{25} and R^{26} each independently represent hydrogen or C_{1-4}alkylcarbonyl;

R^{27} and R^{28} each independently represent hydrogen or C_{1-4}alkylcarbonyl;

Het^1 represents 2-bora-1,3-dioxolanyl;

Het^2 represents piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or 1,1-dioxothiomorpholinyl wherein said Het^2 is optionally substituted with C_{1-4}alkyloxycarbonyl or $NR^{27}R^{28}$-C_{1-4}alkyl; in particular Het^2 represents 1,1-dioxothiomorpholinyl; piperidinyl substituted with C_{1-4}alkyloxycarbonyl; or piperazinyl substituted with C_{1-4}alkyloxycarbonyl or $NR^{27}R^{28}$-C_{1-4}alkyl-;

Het^{25} represents morpholinyl;

Ar^4 represents phenyl;

Ar^5 represents phenyl; or

Ar^6 represents phenyl optionally substituted with nitro.

A further interesting group of compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply :

Z represents NH; Y represents -C_{3-9}alkyl-,-C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-2}alkyl-NR^{21}-H_2-CO-NH-C_{1-3}alkyl- or –C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-;

X^1 represents O or -O-C_{1-2}alkyl-; X^2 represents a direct bond, C_{1-2}alkyl, -CO-C_{1-2}alkyl or NR^{12}-C_{1-2}alkyl;

R^1 represents hydrogen or halo; R^2 represents halo, acetylene or Het^1

R^3 represents hydrogen or cyano; R^4 represents Ar^4-C_{1-4}alkyloxy-, C_{1-4}alkyloxy- or C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from Het^2, NR^7R^8, hydroxy and C_{1-4}alkyloxy-C_{1-4}alkyloxy-;

R^7 represents hydrogen or C_{1-4}alkyl; R^8 represents C_{1-4}alkyl substituted with $NR^{25}R^{26}$ or C_{1-4}alkylsulfonyl;

R^{12} represents hydrogen or C_{1-4}alkyl-; R^{13} represents Ar^6-sulfonyl or C_{1-6}alkyloxycarbonyl optionally substituted with phenyl;

R^{16} and R^{17} represents hydrogen, C_{1-4}alkyl or R^{16} and R^{17} taken together with the carbon atom to which they are attached from a C_{3-6}cycloalkyl;

R^{23} represents C_{1-4}alkyl and R^{23} represents hydrogen when R^{16} and R^{17} taken together with the carbon atom to which they are attached from a C_{3-6}cycloalkyl;

R^{25}, R^{26}, R^{27} and R^{28} each independently represent hydrogen or C_{1-4}alkylcarbonyl;

Het^1 represents 2-bora-1,3-dioxolanyl; Het^2 represents piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or 1,1-dioxothiomorpholinyl wherein said Het^2 is optionally substituted with C_{1-4}alkyloxycarbonyl or $NR^{27}R^{28}$-C_{1-4}alkyl;

Ar^4 and Ar^5 represents phenyl; Ar^6 represents phenyl optionally substituted with nitro.

Other special group of compounds are:

- those compounds of formula (I) wherein -X^1- represents -O-;
- those compounds of formula (I) wherein –X^1- represents C_{1-2}alkyl;
- those compounds of formula (I) wherein –X^1- represents –NR^{11}-, in particular –NH-;
- those compounds of formula (I) wherein –X^2- represents –NR^{12}-C_{1-2}alkyl, in particular –N(CH_3)-C_{1-2}alkyl-;
- those compounds of formula (I) wherein R^1 is fluoro, chloro or bromo;
- those compounds of formula (I) wherein R^2 is fluoro, chloro or bromo;
- those compounds of formula (I) wherein R^2 is Het^1, in particular 2-bora-1,3-dioxolanyl;
- those compounds of formula (I) wherein R^4 is at position 7 of the structure of formula (I).

- those compounds of formula (I) wherein R^4 represents C_{1-4}alkyloxy substituted with hydroxy and one substituent selected from NR^7R^8 or Het^2-;
- those compounds of formula (I) wherein R^7 is hydrogen or methyl and R^8 represents aminocarbonyl-C_{1-4}alkyl-, $NR^{25}R^{26}$, C_{1-4}alkylsulfonyl-C_{1-4}alkyl-, C_{1-4}alkylcarbonyloxy-C_{1-4}alkyl or Het^{11}-C_{1-4}alkyl-; in particular those compounds of formula (I) wherein R^7 is hydrogen or methyl and R^8 represents aminocarbonyl-C_{1-4}alkyl-, $NR^{25}R^{26}$, C_{1-4}alkylsulfonyl-C_{1-4}alkyl- or Het^{11}-C_{1-4}alkyl-
- those compounds of formula (I) wherein Het^2 represent piperidinyl, 1,1-dioxothiomorpholinyl or piperazinyl and said Het^2 is optionally substituted with one or where possible two or more substituents selected from $NR^{39}R^{40}$, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl or C_{1-4}alkylsulfonyl; in particular those compounds of formula (I) wherein Het^2 represent piperidinyl or piperazinyl and said Het^2 is optionally substituted with one or where possible two or more substituents selected from $NR^{39}R^{40}$, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl or C_{1-4}alkylsulfonyl.

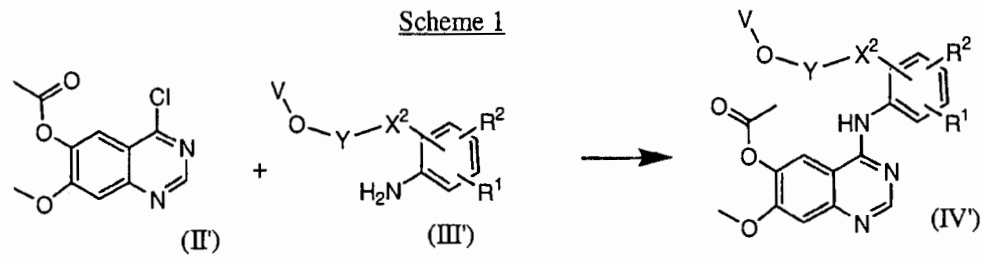
In a further embodiment of the present invention the X^2 substituent is at position 2', the R^1 substituent represents hydrogen or halo and is at position 4', the R^2 substituent represents halo and is at position 5', the R^3 substituent is at position 2 and the R^4 substituent at position 7 of the structure of formula (I). Alternatively, the X^2 substituent is at position 3', the R^1 substituent represents hydrogen or halo and is at position 4', the R^2 substituent represents halo and is at position 5', the R^3 substituent is at position 2 and the R^4 substituent at position 7 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 described for instance 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.

As further exemplified in the experimental part of the description, a particular group of compounds are those compounds of formula (I) were -X^1- represents -O- hereinafter referred to as the compounds of formula (3). Said compounds are generally prepared starting from the known 6-acetoxy-4-chloro-7-methoxy quinazoline (II') which can be prepared from commercially available veratric acid and 4-hydroxy-3-methoxy benzoic acid, respectively.

Coupling of the latter with suitable substituted anilines (III') under standard conditions, for example stirred in 2-propanol at an elevated temperature ranging form 40-100°C during 3-12 h, furnish the intermediate compounds (IV') (Scheme 1).

Scheme 1

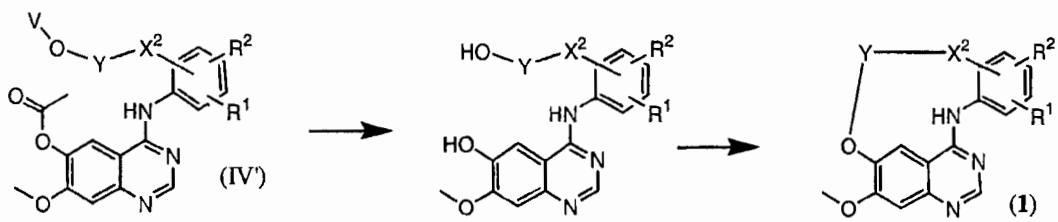


V = hydrogen or a protective group such as for example, methylcarbonyl, t-butyl, methyl, ethyl, benzyl or trialkylsilyl groups

X^2, R^1 and R^2 are defined as for the compounds of formula (I)

Deprotection of the intermediates of formula (IV') as described in *Protective Groups in Organic Synthesis by T.W. Greene and P.G.M. Wuts, 3rd edition, 1998* followed by ring closure under Mitsunobu conditions give the macrocyclic compounds (**1**) that are used as starting compounds in the synthesis of the final compounds of the present invention. (Scheme 2 – wherein V is defined as hereinbefore).

Scheme 2a

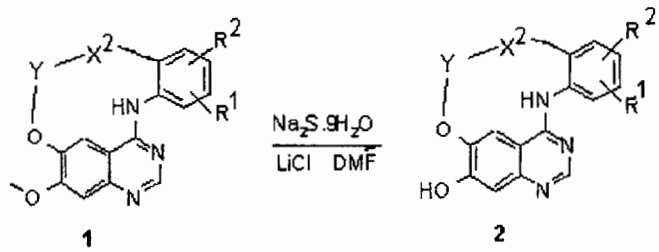


V = hydrogen or a protective group such as for example, methylcarbonyl, t-butyl, methyl, ethyl, benzyl or trialkylsilyl groups

X^2, R^1 and R^2 are defined as for the compounds of formula (I)

In brief, said macrocyclic compounds of formula (**1**) are demethylated using art known conditions such as for example provided in Schemes 3&4 hereinbelow, followed by an alkylation with an appropriate alcohol, such as for example described in Scheme 5 hereinafter.

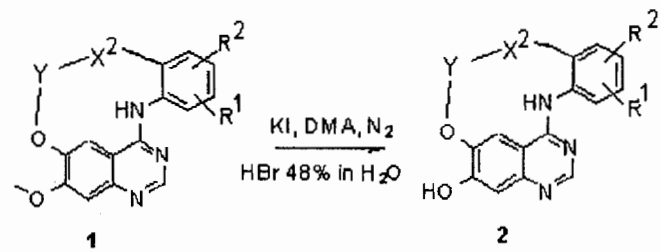
Quinazoline demethylation. Scheme 3:



1 2

A stirred suspension of **1** (1 equiv), LiCl (7 equiv.) and $Na_2S.9H_2O$ (7 equiv) in DMF, was heated under microwave conditions to 140° C until completion (30 minutes). The reaction mixture was allowed to cool to ambient temperature and was then poured onto ice water. The mixture was filtered and the yellow precipitation was re-dissolved in DCM/MeOH (9:1) with some HCOOH and purified over silica gel filter (eluens: DCM/MeOH 9.5/0.5). The pure fractions were collected, evaporated and co-evaporated with toluene to give pure **2** (yield: 70 %).

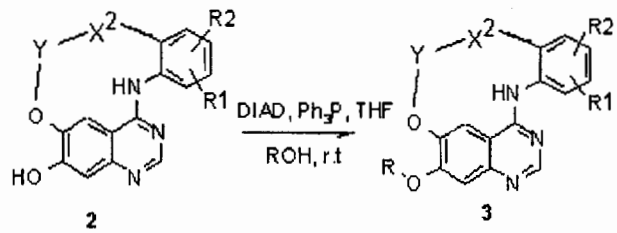
Quinazoline demethylation. Scheme 4:



1 2

To a stirred suspension of **1** (1 equiv) and KI (10 equiv) in DMA, was added HBr (48 % in H_2O) while bubbling N_2 through the reaction mixture. The mixture was rapidly heated to 130° C and stirred at this temperature until completion (± 2h). The reaction mixture was allowed to cool to 70° C and poured onto ice/H_2O/NH_3. The mixture was filtered and the yellow precipitation was re-dissolved in THF/MeOH (2:1), concentrated and co-evaporated with toluene. Crystalization from 2-propanol afford pure **2** (yield : 42 – 78 %).

Quinazoline alkylation. Scheme 5

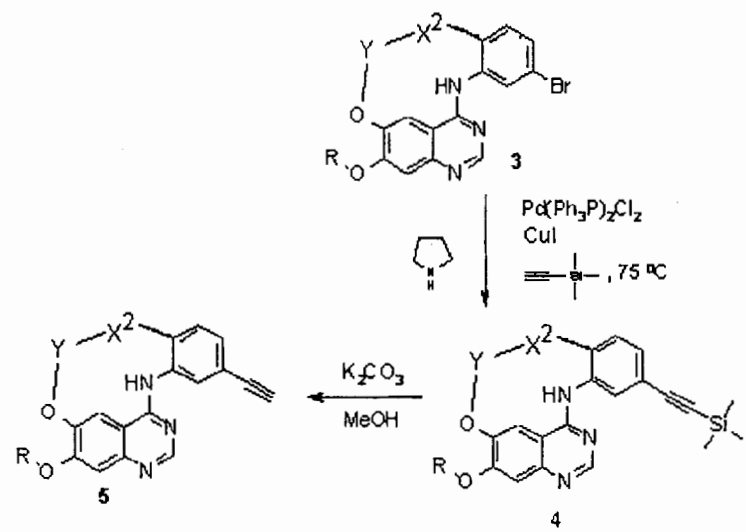


wherein R represents Ar^4-C_{1-4}alkyl-, C_{1-4}alkyl- or R represents C_{1-4}alkyl substituted with one or where possible two or more substituents selected from hydroxy, halo, C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy-, NR^7R^8 or Het^2-. Ar^4, Het^2, R^7 and R^8 are defined as for the compounds of formula (I) hereinbefore.

To a stirred suspension of **2** (1 equiv), alcohol (8 equiv) and triphenylphosphine (2 equiv) in THF, DIAD (2 equiv) was added dropwise and the mixture was stirred at room temperature for 60 min. The reaction mixture was concentrated under reduced pressure, and the crude product was triturated from acetonitrile to afford pure **3**.

For those compounds of formula (**3**) wherein R^1 or R^2 represent acetylene the following synthesis scheme (Scheme 6) is generally applied. In brief, the halogenated form of the compounds of formula (**3**) is acetylated using trimethylsilylacetylene followed by deprotection of the acetylene group to yield the compounds of general formula (**5**).

Incorporation of acetylene moiety. Scheme 6



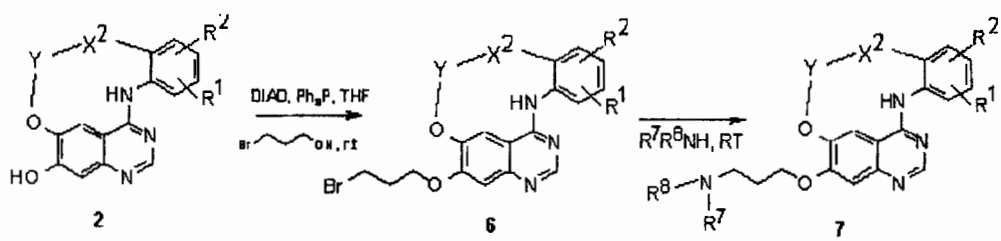
wherein R is defined as in Scheme 5 hereinbefore

To a stirred solution of **3** (1 equiv) in pyrrolidine was added bis(triphenylphosphine)palladium(II)chloride (20 mol%) followed by CuI (cat). The reaction mixture was heated to 75°C and trimethylsilylacetylene (2.5 equiv) was added. The mixture was stirred at this temperature until the reaction was essentially complete and was then filtered through a short pad of celite and concentrated to dryness. The residue was re-dissolved in EtOAc and was partitioned between EtOAc and water. The combined organic layers were concentrated under reduced pressure and the residue was treated with MP-TMT in acetonitrile overnight. It was then filtered, the resin was washed with acetonitrile followed by DCM and the filtrate was concentrated to afford **4**.

Compound **4** and aqueous K_2CO_3 (sat.) in MeOH (1:1) were stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, the residue was re-dissolved in DCM and washed with water. The organic phase was separated, dried ($MgSO_4$) and concentrated under vaccuo. The residue was purified either by column chromatography or reverse phase HPLC to afford pure **5**.

A particular group of compounds are those compounds of formula (**3**) wherein R represents C_{1-4}alkyl substituted with NR^7R^8 or Het^2 wherein said Het^2 is attached to the remainder of the molecule through the nitrogen atom. Said compounds of general formula (**7**) are generally made according to synthesis scheme 7 departing from the intermediate compounds of general formula (**2**).

Scheme 7



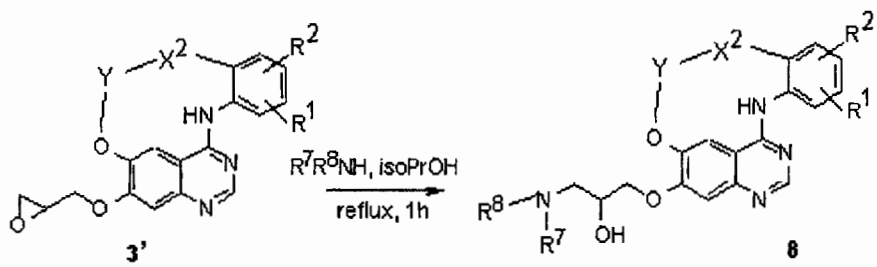
wherein R^7 and R^8 are defined as for the compounds of formula (I), or R^7 and R^8 taken together with the nitrogen atom to which they are attached from a heterocycle wherein said heterocycle is defined as Het^2 for the compounds of formula (I) hereinbefore.

To a stirred suspension of **2** (1 equiv), bromopropyl alcohol (2 equiv) and triphenylphosphine (2 equiv) in THF, DIAD (2 equiv) was added dropwise and the mixture was stirred at room temperature for 60 min. The reaction mixture was concentrated under vaccuo, and the crude product was triturated from acetonitrile to afford pure **6**.

To a stirred suspension of **6** (1 equiv), in acetonitrile was added the amine (20 equiv) and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vaccuo, and the crude product was triturated from acetonitrile to afford pure **7**.

Alternatively to the above, and in particular for those compounds of formula (**7**) wherein the C_{1-4}alkyl moiety is further substituted with hydroxy-, said compounds are made using a nucleophilic addition reaction departing from the oxirane analog **3'** (Scheme 8)

Scheme 8



Wherein R^7 and R^8 are defined as for the compounds of formula (I), or R^7 and R^8 taken together with the nitrogen atom to which they are attached from a heterocycle wherein said heterocycle is defined as Het^2 for the compounds of formula (I) hereinbefore.

To a stirred suspension of **3'** (1 equiv), in 2-propanol was added the amine (20 equiv) and the mixture was stirred at 70° C for 2 hours. The reaction mixture was cooled, and the product crystallized from 2-propanol to afford pure **8**.

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.

Additionally, the N-atoms in compounds of formula (I) can be methylated by art-known methods using CH_3-I in a suitable solvent such as, for example 2-propanone, tetrahydrofuran or dimethylformamide.

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.

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 peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic 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. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as fractional crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

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 art-known procedures. For example, diastereoisomers can be separated by physical methods such as fractional 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 or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, fractional rystallization 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.

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.

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.

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 such as for example EGFR, Abl, Fyn, FlT1, HcK or the Sar kinase family such as for example Lyn, Yes and cSRC. In an alternative assay, the growth inhibitory effect of the compounds was tested on a number of carcinamo cell lines, in 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 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.

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, a method of treating a cell proliferative disorder such as atherosclerosis, restenosis and cancer is provided, 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.

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 EGFR 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 EGFR inhibitor to be administered as a 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 EGFR inhibitor at the treatment site in the range of 0.5 nM to 200 μM, and more usually 5 nM to 10 μM. To obtain these treatment concentrations, a patient in need of treatment likely will be administered between 0.01 mg/kg to 300 mg/kg body weight, in particular from 10 mg/kg to 100 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, suitable pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients.

Due to their high degree of selectivity as EGFR inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify the kinase domain within the receptor tyrosine kinase receptors. To this purpose, the compounds of the present invention can be labelled, in particular by replacing, partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds having at least one ^{11}C-atom or tritium atom.

One particular group consists of those compounds of formula (I) wherein R^1 is a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable isotope. Suitable halogen radioisotopes to this purpose are radioactive iodides, e.g. ^{122}I, ^{123}I, ^{125}I, ^{131}I; radioactive bromides, e.g. ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br, and radioactive fluorides, e.g. ^{18}F. The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

Another interesting form of radiolabelling is by substituting a carbon atom by a ^{11}C-atom or the substitution of a hydrogen atom by a tritium atom.

Hence, said radiolabelled compounds of formula (I) can be used in a process of specifically marking receptor sites in biological material. Said process comprises the steps of (a) radiolabelling a compound of formula (I), (b) administering this radiolabelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound.

Alternatively the compounds are labeled with stable isotopes. In this form of labeling the naturally abundant isotopes of hydrogen, carbon and nitrogen (^{1}H, ^{12}C and ^{14}N) are replaced with stable isotopes of these elements (^{2}H [deuterium], ^{13}C and ^{15}N, respectively). Labeling with stable isotopes is used for two principal purposes:

- Incorporation of stable isotopes into proteins, carbohydrates and nucleic acids facilitates their structural determination at the atomic level.
- Metabolic studies exploiting the increased mass of compounds labeled with stable isotopes

The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term refers to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.

When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution to the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of formula (I) and detecting the emissions from the radioactive compound also constitutes a part of the present invention.

In yet a further aspect, the present invention provides the use of the compounds 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, of 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 300 mg/kg body weight, in particular from 10 mg/kg to 100 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 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 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 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 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, 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 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 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 wetting 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 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 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 segregated multiples thereof.

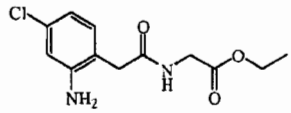
Experimental part

Hereinafter, the term 'THF' means tetrahydrofuran, 'DIPE' means diisopropyl ether, 'DMF' means *N,N*-dimethylformamide, 'NaBH(OAc)$_3$' means sodium triacetoxyborohydride, 'EtOAc' means ethyl acetate, 'EDCI' means *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine monohydrochloride, 'HOBT' means 1-hydroxy-1H-benzotriazole, 'CDI' means 1,1'-carbonylbis-1H-imidazole, 'DIPEA' means *N*-ethyl-*N*-(1-methylethyl)- 2-propanamine, 'NaBH$_4$' means sodium tetrahydroborate(-1), 'DMA' means dimethylacetamide, 'DIAD' means bis(1-methylethyl) ester diazenedicarboxylic acid, 'HBTU' means 1-[bis(dimethylamino)methylene]-1H-Benzotriazoliumhexafluorophosphate(1-)3-oxide, 'HATU' means 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide, hexafluorophosphate(1-), 'HOAT' means 3-hydroxy-3H-1,2,3-triazolo[4,5-b]pyridine

A. Preparation of the intermediates

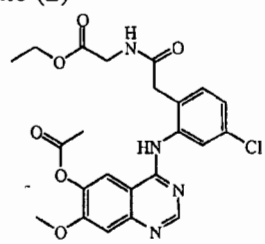
Example A1

a) Preparation of intermediate (1)



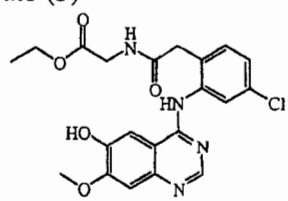
A mixture of *N*-[(4-chloro-2-nitrophenyl)acetyl]glycine ethyl ester (0.023 mol) in THF (250ml) was hydrogenated with Pt/C (2.0 g) as a catalyst in the presence of a 4% thiophene solution in DIPE (1ml). After uptake of H_2 (3 equiv.), the catalyst was filtered off and the filtrate was evaporated. The obtained residue was suspended in DIPE, then the suspension was stirred at boiling temperature, cooled and the desired product was collected by filtration, yielding 6.2g (100%) of intermediate (1).

b) Preparation of intermediate (2)



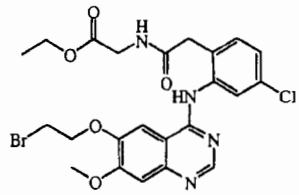
A mixture of 4-chloro-7-methoxy-6-quinazolinol acetate ester (0.00050 mol) and intermediate (1) (0.00050 mol) in 2-propanol (5ml) was stirred for 16 hours in a pressure tube at 80°C (oil bath temperature), then the reaction mixture was filtered and the filter residue was air-dried, yielding 0.165g (67.7%) of intermediate (2).

c) Preparation of intermediate (3)



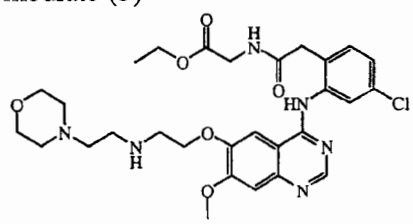
A mixture of intermediate (2) (0.0244 mol) in NH_3/CH_3OH (7N) (50ml) and CH_3OH (100ml) was stirred overnight at room temperature and then the solvent was evaporated (Genevac.) under reduced pressure and at room temperature. Finally, the obtained residue was dried (vac.) overnight at 60°C, yielding 8.2g (75%) of intermediate (3).

d) Preparation of intermediate (4)



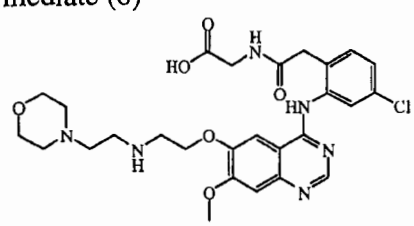
A mixture of intermediate (3) (0.0138 mol) and Cs_2CO_3 (0.0690 mol) in DMF (120ml) was stirred for 30 minutes at room temperature, then 1,2-dibromoethane (0.117 mol) was added and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residue was co-evaporated with toluene. The obtained residue was stirred in DIPE and the desired product was filtered off, yielding 6.93g (91%) of intermediate (4).

e) Preparation of intermediate (5)



A mixture of intermediate (4) (0.00181 mol) and 4-morpholineethanamine (0.00907 mol) in ethanol (20ml) was heated in a microwave oven for 90 minutes at 100°C and then the reaction mixture was purified by reversed-phase high-performance liquid chromatography. The product fractions were collected and the solvent was evaporated, yielding 0.39g (36%) of intermediate (5).

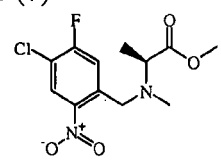
f) Preparation of intermediate (6)



A mixture of intermediate (5) (0.00065 mol) and lithium hydroxide (0.0032 mol) in ethanol (20ml) and H_2O (2ml) was stirred for 2 hours at room temperature and then the solvent was evaporated under reduced pressure, yielding intermediate (6) (quantitative yield).

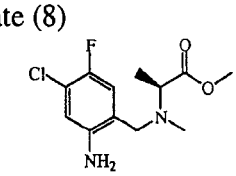
Example A2

a) Preparation of intermediate (7)



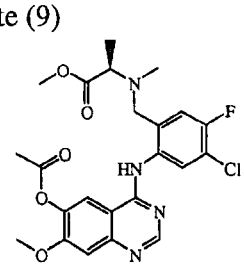
A mixture of 4-chloro-5-fluoro-2-nitrobenzaldehyde (0.0491 mol), *N*-methyl-L-alanine methyl ester hydrochloride (0.0589 mol) and titanium(4+) 2-propanol salt (0.0737 mol) in 1,2-dichloroethane (100ml) was stirred at room temperature for 30 minutes. $NaBH(OAc)_3$ (0.0589 mol) was added. The mixture was stirred overnight, then diluted in CH_2Cl_2, quenched with aqueous (10%) K_2CO_3 and filtered. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated to dryness, yielding 16.5g (quantitative yield) of intermediate (7) (S-configuration).

b) Preparation of intermediate (8)



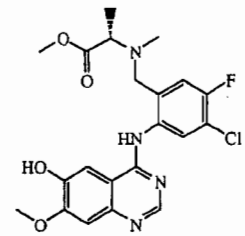
A mixture of intermediate (7) (0.0491 mol), Fe (0.246 mol) and NH_4Cl (0.491 mol) in THF/CH_3OH/H_2O (4/4/2; 500ml) was stirred and refluxed overnight, then cooled to room temperature and filtered. The filtrate was diluted in CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness, yielding 13g (96%) of intermediate (8) (S-configuration).

c) Preparation of intermediate (9)



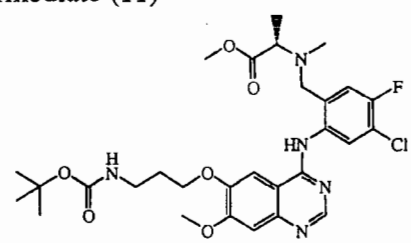
A mixture of 4-chloro-7-methoxy-6-quinazolinol acetate ester (0.0162 mol) and intermediate (8) (0.0162 mol) in CH_3CN (150ml) was stirred and refluxed for 4 hours, then cooled back to room temperature, the solvent was evaporated in vacuo and the residue was taken up in K_2CO_3 (aq.) (10%) and CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated to dryness. The residue (6.4g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0 to 99/1; 15-40μm). The desired fractions were collected and the solvent was evaporated, yielding 3.09g (37%) of intermediate (9) (S-configuration).

d) Preparation of intermediate (10)



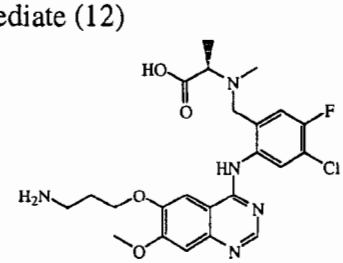
A mixture of intermediate (9) (0.0061 mol) in NH_3/CH_3OH (7N) (20ml) and CH_3OH (100ml) was stirred at room temperature for 40 hours, then evaporated to dryness. The residue was taken up in CH_3CN/DIPE. The precipitate was filtered off and dried, yielding 1.93g (70%) of intermediate (10) (M.P.: 234°C; S-configuration).

e) Preparation of intermediate (11)



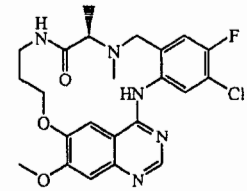
Cs_2CO_3 (0.0063 mol) was added to a solution of intermediate (10) (0.0042 mol) in dry DMF (20ml). The mixture was stirred at room temperature for 1 hour. A solution of (3-bromopropyl)-1,1-dimethylethyl ester carbamic acid (0.0046 mol) in dry DMF (5ml) was added. The mixture was stirred at room temperature for 3 hours, poured into H_2O and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated to dryness, yielding: 2.8g (quantitative yield) of intermediate (11) (S-configuration).

f) Preparation of intermediate (12)



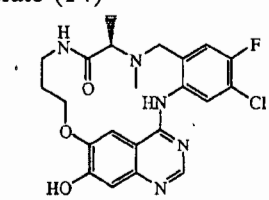
A mixture of intermediate (11) (0.0042 mol) in HCl (aq.) (6N) (20ml) and dioxane (100ml) was stirred at 60°C for 3 hours, then cooled to room temperature and evaporated to dryness. The residue was taken up in ethanol/diethyl ether. The precipitate was filtered under N_2 flow and dried in vacuo, yielding 2.24g (100%) of intermediate (12) as a hydrochloric acid salt(.3.02HCl .1.88H_2O; S-configuration; M.P.: 175°C).

g) Preparation of intermediate (13)



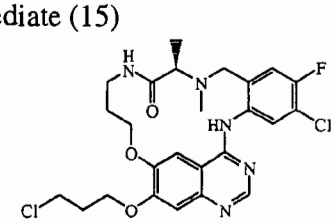
Intermediate (12) (0.0018 mol) was added portionwise to a warm solution (50°C) of EDCI (0.0037 mol), HOBT (0.0037 mol) and triethylamine (0.008 mol) in CH_2Cl_2/THF (50/50; 1000ml) over a 3 hour period, under vigorous stirring at 50°C. After evaporation of the solvent, the residue was taken up in K_2CO_3 (aq.) (10%). The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness. The residue (1g) was crystallized from ethanol/DIPE. The precipitate was filtered off and dried. This fraction was crystallized again from CH_3CN. The precipitate was filtered off and dried, yielding 0.21g (24%) of intermediate (13) (M.P.: 270°C; S-configuration).

h) Preparation of intermediate (14)



A mixture of intermediate (13) (0.0001 mol), sodium sulfide (0.001 mol) and lithium chloride (0.0011 mol) in DMF (1ml) was stirred at room temperature for 5 minutes, then heated in a microwave oven at 90°C for 15 minutes, poured into saturated $NaHCO_3$ and extracted with diethyl ether three times. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness. The residue (1.3g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0 to 90/10; 15-40μm). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 0.406g (84%) of intermediate (14) (M.P.: 196°C; S-configuration).

i) Preparation of intermediate (15)

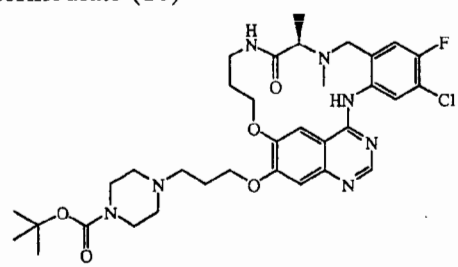


1-Bromo-3-chloropropane (0.0012 mol) was added to a suspension of intermediate (14) (0.0008 mol) and K_2CO_3 (aq.) (0.0016 mol) in CH_3CN/DMF (8ml). The mixture was stirred and refluxed for 18 hours, then cooled to room temperature, poured into H_2O

and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness. The residue (0.85g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0 to 97/3; 15-40μm). The pure fractions were collected and the solvent was evaporated, yielding 0.24g (58%) of intermediate (15) (S-configuration).

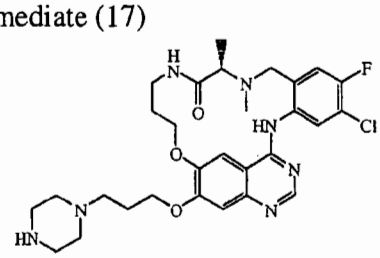
Example A3

a) Preparation of intermediate (16)



A mixture of intermediate (15) (0.0005 mol), 1,1-dimethylethyl ester 1-piperazinecarboxylic acid (0.001 mol) and K_2CO_3 (aq.) (0.0005 mol) in CH_3CN (3ml) was stirred and refluxed overnight. 1,1-Dimethylethyl ester 1-piperazinecarboxylic acid (0.001 mol) and K_2CO_3 (aq.) (0.0005 mol) were added again. The mixture was stirred and refluxed for 18 hours, cooled to room temperature, poured into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness. The residue (0.487g) was purified by column chromatography over kromasil (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 99/1/0.05 to 90/10/0.5; 5μm). The pure fractions were collected and the solvent was evaporated, yielding 0.165g (46%) of intermediate (16) (S-configuration; M.P.: 140°C).

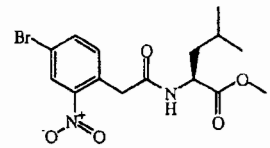
b) Preparation of intermediate (17)



HCl/2-propanol (0.3ml) was added to a mixture of intermediate (16) (0.0001 mol) in CH_3OH (3ml). The mixture was stirred at room temperature overnight, then stirred at room temperature for 18 extra hours and evaporated to dryness. This hydrochloric acid salt was taken up in K_2CO_3 (aq.) (10%). The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness, yielding: 0.095g (100%) of intermediate (17) (S-configuration).

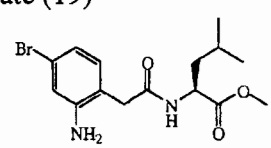
Example A4

a) Preparation of intermediate (18)



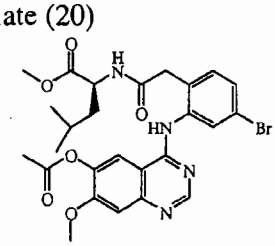
A mixture of 4-bromo-2-nitrobenzeneacetic acid (0.077 mol) and HOBT (0.077 mol) in CH_2Cl_2 (550ml) was stirred at room temperature. CDI (0.077 mol) was added and stirring was continued for 10 minutes. Then DIPEA (0.077 mol) was added and the reaction mixture was stirred at room temperature for 30 minutes. L-Leucine methyl ester hydrochloride (0.077 mol) was added at once and the mixture was stirred overnight at room temperature. An extra amount of HOBT (0.077 mol), CDI (0.077 mol) and DIPEA (0.077 mol) was added and the reaction mixture was stirred at room temperature over the weekend. The mixture was quenched with H_2O and the layers were separated. The organic layer was washed with saturated K_2CO_3 (aq.) (1x) and HCl (1N) (1x), then dried ($MgSO_4$), filtered and the solvent was evaporated. The red gum-like product was triturated from 2-propanol. The off-white solid was filtered off and dried, yielding 7.87g of intermediate (18) (S-configuration).

b) Preparation of intermediate (19)



A mixture of intermediate (18) (0.056 mol) in toluene (219ml) was stirred (mixture (1)). A mixture of NH_4Cl (0.283 mol) in H_2O (151ml) was added to mixture (1) and in a next step Fe (0.283 mol) was added. The reaction mixture was refluxed overnight. Then another portion of NH_4Cl (0.283 mol) and Fe (0.283 mol) was added and the reaction mixture was refluxed for 1 hour. The mixture was cooled to room temperature and then filtered through dicalite. The layers were separated and the aqueous layer was washed with toluene. The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 20.1g of intermediate (19) (S-configuration).

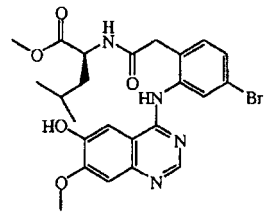
c) Preparation of intermediate (20)



A solution of intermediate (19) (0.055 mol) in 2-propanol (200ml) was heated to 70°C (solution (1)). A solution of 4-chloro-7-methoxy-6-quinazolinol acetate ester (0.066

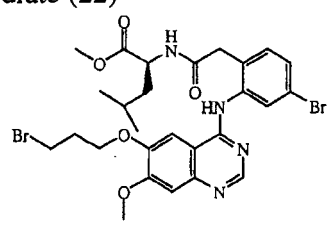
mol) in 2-propanol (200ml) was also heated to 70°C and this solution was added to solution (1). Stirring at 70°C was continued for 75 minutes. An extra amount of 4-chloro-7-methoxy-6-quinazolinol acetate ester (0.027 mol) in 2-propanol (100ml) was added and the mixture was reacted further for 2 hours. The solvent was evaporated and the residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99.5/0.5 till 90/10). The product fractions were collected and the solvent was evaporated, yielding 13.82g of intermediate (20) (S-configuration).

d) Preparation of intermediate (21)



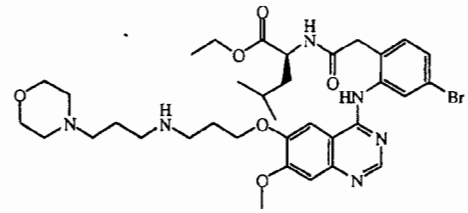
A mixture of intermediate (20) (0.081 mol) in CH_3OH (400ml) was stirred at room temperature. NH_3/CH_3OH (7N) (200ml) was added and the reaction mixture was stirred at room temperature for 95 minutes. The solvent was evaporated and the residue was triturated from 2-propanol. The pale yellow solid was filtered off and dried, yielding 43g (99.9%) of intermediate (21) (S-configuration).

e) Preparation of intermediate (22)



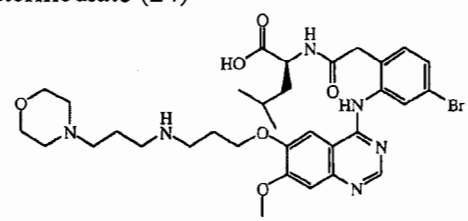
A mixture of intermediate (21) (0.0113 mol) in DMF (300ml) was stirred. K_2CO_3 (aq.) (0.056 mol) was added and the reaction mixture was stirred at room temperature for 35 minutes. Then 1,3-dibromopropane (0.113 mol) was added and the reaction mixture was stirred for 40 hours at room temperature. The reaction mixture was filtered and concentrated under reduced pressure till ~20ml. The concentrate was poured into H_2O and the precipitation was filtered off and dried, yielding 7.16g (97.1%) of intermediate (22) (S-configuration).

f) Preparation of intermediate (23)



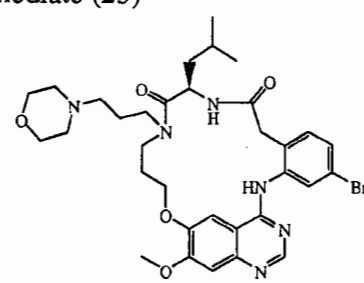
A mixture of intermediate (22) (0.003832 mol) and 4-morpholinepropanamine (0.0383 mol) in ethanol (40ml) was heated to 100°C for 1 hour and then purified by high performance liquid chromatography. The organic solvent was evaporated and the water layer was concentrated to ~20ml. The concentrate was made alkaline with aqueous NaOH (1N) to a pH of ~10 and extracted with EtOAc. The separated organic layer was dried ($MgSO_4$), filtered and the mixture was concentrated, yielding 9.14g of intermediate (23) (S-configuration).

g) Preparation of intermediate (24)



A mixture of intermediate (23) (0.007909 mol) in CH_3OH (40ml) and H_2O (4ml) was stirred at room temperature until dissolution. Lithium hydroxide (0.0395 mol) was added and the reaction mixture was stirred for 85 minutes. The reaction mixture was concentrated and the residue was dried, yielding 5.53 g (99.6%) of intermediate (24) (S-configuration).

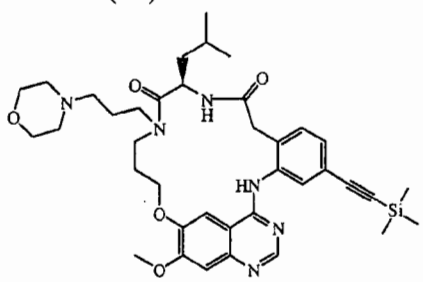
h) Preparation of intermediate (25)



A mixture of HATU (0.002052 mol) and HOAT (0.00008551 mol) in DMA (50ml) was added dropwise to a mixture of intermediate (24) (0.0007126 mol) and DIPEA (0.002138 mol) in DMA (50ml). The reaction mixture was stirred overnight. H_2O was added and the mixture was concentrated to ~10ml. EtOAc was added to the mixture to become a solution. H_2O was added and the two layers were separated. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The obtained residue was purified by high performance liquid chromatography (NH_4HCO_3 buffer). The

product fractions were collected, the solvent was evaporated and the residue was dried, yielding intermediate (25) (S-configuration; quantitative yield).

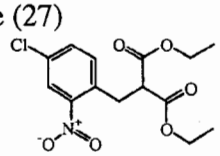
i) Preparation of intermediate (26)



A mixture of intermediate (25) (0.0007314 mol) in pyrrolidine (10ml) was stirred dichlorobis(triphenylphosphine)palladium (0.00003657 mol) and copper iodide (catalytic amount) were added and the reaction mixture was heated to 75°C. Ethynyltrimethylsilane (0.001828 mol) was added and heating was continued for 30 minutes. Then an extra portion of dichlorobis(triphenylphosphine)palladium (0.00003657 mol) and ethynyltrimethylsilane (0.001828 mol) was added and the mixture was reacted for 270 minutes. The reaction mixture was filtered through celite and washed with CH_3OH. The solvent was evaporated and the residue was redissolved in EtOAc and washed 2x with H_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The crude residue was redissolved in CH_3CN and MP-TMT resin (0.0003657 mol) was added to scavenge any residual Pd. This mixture was stirred for 36 hours at room temperature and was then filtered. The resin was washed with CH_3OH and the filtrate was evaporated, yielding 0.48 g of intermediate (26) (S-configuration).

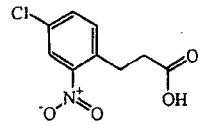
Example A5

a) Preparation of intermediate (27)



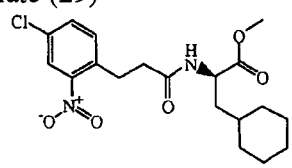
4-Chloro-1-(chloromethyl)-2-nitrobenzene (0.81 mol) and propanedioic acid diethyl ester (0.794 mol) were suspended in hexane (300ml). K_2CO_3 (aq.) (0.81 mol) was added. Then, 18-crown-6 (0.008 mol) was added. The resultant reaction mixture was stirred and refluxed for 30 hours under N_2 atmosphere. The reaction mixture was cooled to 20°C. This mixture was extracted with water (750ml). The layers were separated. The aqueous phase was washed with toluene. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was evaporated, yielding 255.8g of intermediate (27).

b) Preparation of intermediate (28)



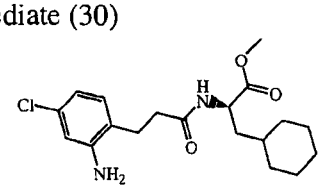
Intermediate (27) (255.8g, 0.466 mol) was dissolved in acetic acid (1000ml). A 20% aqueous HCl solution (1000ml) was added and the resulting reaction mixture was stirred and refluxed for 16 hours. The reaction mixture was cooled to 20°C and the solvent was evaporated. The residue was suspended in water (500ml) and treated with a 10% aqueous NaOH solution (500ml). This mixture was stirred for one hour. This mixture was extracted with diethyl ether (3 x 500ml) and then acidified with concentrated HCl resulting in precipitation from the cooled aqueous layer. The precipitate was filtered off and dried, yielding 109g of intermediate (28) (M.P.: 109-111°C).

c) Preparation of intermediate (29)



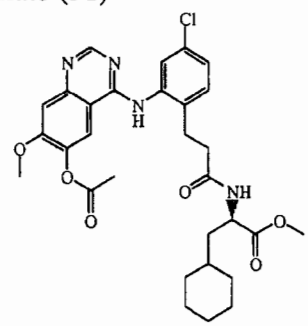
A mixture of intermediate (28) (0.015 mol) and HOBT (0.015 mol) in CH_2Cl_2 (10ml) was stirred for 30 minutes at room temperature. CDI (0.015 mol) was added and the reaction mixture was stirred for 30 minutes at room temperature. The resultant solution was added to a mixture of α-aminocyclohexanepropanoic acid methyl ester hydrochloride (0.01875 mol) and diisopropylmethylamine/resin (1 0.05 mol) in CH_2Cl_2 (70ml) and the reaction mixture was shaken overnight at room temperature. An excess of scavenger resins (polystyrylmethyl)trimethylammonium bicarbonate and sulfonic acid resin MP (70-90 mesh) were added and the mixture was shaken for 18 hours. The mixture was filtered. The filtrate was concentrated at room temperature, yielding intermediate (29) (S-configuration; quantitative yield).

d) Preparation of intermediate (30)



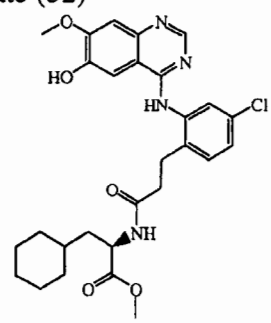
A mixture of intermediate (29) (0.001 mol) in 2-propanol (20ml) was hydrogenated with 5% Pt/C (catalytic quantity) as a catalyst in the presence of vanadium oxide (q.s.) and a 4% thiophene solution in DIPE (q.s.). After uptake of H_2 (3 equiv), the catalyst was filtered off and the filtrate was evaporated, yielding intermediate (30) (S-configuration; quantitative yield).

e) Preparation of intermediate (31)



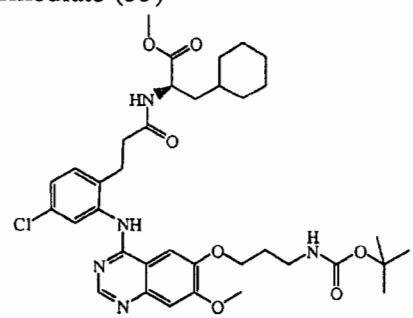
A mixture of 4-chloro-7-methoxy-6-quinazolinol acetate ester (0.001 mol) and intermediate (30) (1 equiv; 0.001 mol) in 2-propanol (25ml) was stirred for 6 hours at 80°C. The reaction mixture was cooled to room temperature and used as such in next reaction step, yielding intermediate (31) (S-configuration; quantitative yield).

f) Preparation of intermediate (32)



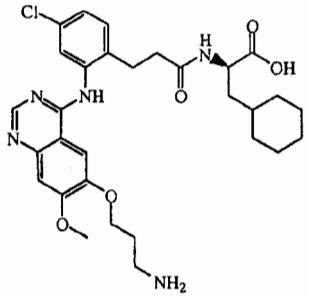
A mixture of intermediate (31) (0.0010 mol) in 2-propanol (25ml) and NH_3/CH_3OH (5ml) was stirred for 18 hours at room temperature. The solvent was evaporated under reduced pressure. The residue was purified by high-performance liquid chromatography. The product fractions were collected and the solvent was evaporated, yielding intermediate (32) (S-configuration; quantitative yield).

g) Preparation of intermediate (33)



A mixture of intermediate (32) (crude) and Cs_2CO_3 (5 equiv.) in DMF (5ml) was stirred for 30 minutes at room temperature. (3-bromopropyl)-1,1-dimethylethyl ester carbamic acid (1.1 equiv.) was added and the reaction mixture was stirred for 18 hours at room temperature. The solvent was evaporated under reduced pressure, yielding intermediate (33) (S-configuration; quantitative yield).

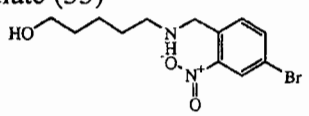
h) Preparation of intermediate (34)



A solution of intermediate (33) (crude) in HCl (6N) (2ml) and dioxane (2ml) was stirred for 16 hours at 60°C. The solvent was evaporated under reduced pressure, yielding of intermediate (34) (S-configuration; quantitative yield).

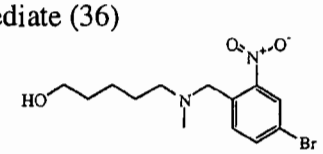
Example A6

a) Preparation of intermediate (35)



A solution of 4-bromo-2-nitrobenzaldehyde (0.013 mol), 5-amino-1-pentanol (0.013 mol) and titanium(4+) 2-propanol salt (0.014 mol) in ethanol (15ml) was stirred at room temperature for 1 hour, then the reaction mixture was heated to 50°C and stirred for 30 minutes. The mixture was cooled to room temperature and $NaBH_4$ (0.013 mol) was added portionwise. The reaction mixture was stirred overnight and then poured onto ice water (50ml). The resulting mixture was stirred for 20 minutes, the formed precipitate was filtered off (giving Filtrate (I)), washed with H_2O and stirred in CH_2Cl_2 (to dissolve the product and to remove it from the Ti-salt). The mixture was filtered and then the filtrate was dried ($MgSO_4$) and filtered, finally the solvent was evaporated to dryness. Filtrate (I) was evaporated until ethanol was removed and the aqueous concentrate was extracted 2 times with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated dry, yielding 3.8 g (93%) of intermediate (35).

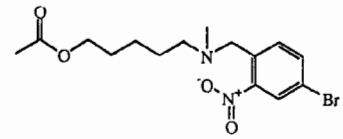
b) Preparation of intermediate (36)



A solution of intermediate (35) (0.0047 mol), formaldehyde (0.025 mol) and titanium(4+) 2-propanol salt (0.0051 mol) in ethanol (150ml) was heated to 50°C and stirred for 1 hour, then $NaBH_4$ (0.026 mol) was added portionwise at room temperature. The reaction mixture was stirred overnight and then quenched with water (100ml). The resulting mixture was stirred for 1 hour; the formed precipitate was filtered off and

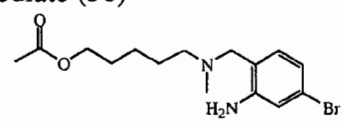
washed. The organic filtrate was concentrated, then the aqueous concentrate was extracted with CH_2Cl_2 and dried. The solvent was evaporated dry and the residue was filtered over silica gel (eluent: CH_2Cl_2/CH_3OH from 98/2 to 95/5). The product fractions were collected and the solvent was evaporated dry, yielding 0.5g of intermediate (36).

c) Preparation of intermediate (37)



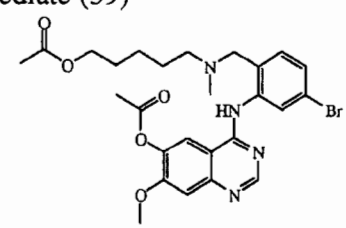
A solution of intermediate (36) (0.0015 mol) and pyridine (0.015 mol) in acetic acid anhydride (8ml) was stirred overnight at room temperature, then the solvent was evaporated and co-evaporated with toluene, yielding intermediate (37) (quantitative yield).

d) Preparation of intermediate (38)



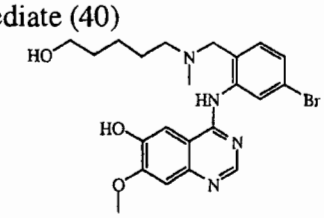
A mixture of intermediate (37) (0.0015 mol) in THF (50ml) was hydrogenated with 5% Pt/C (0.5 g) as a catalyst in the presence of a 4% thiophene solution in DIPE (0.5ml). After uptake of H_2 (3 equiv.), the catalyst was filtered off and the filtrate was evaporated, yielding 0.5g of intermediate (38).

e) Preparation of intermediate (39)



A mixture of intermediate (38) (0.0015 mol) and 4-chloro-7-methoxy-6-quinazolinol acetate ester (0.0015 mol) in 2-propanol (30ml) was heated to 80°C and the reaction mixture was stirred for 1 day. The solvent was evaporated under reduced pressure, yielding 0.83g of intermediate (39).

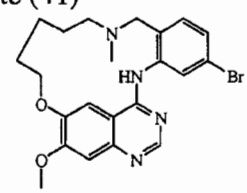
f) Preparation of intermediate (40)



A solution of intermediate (39) (0.0015 mol) in CH_3OH (25ml) was stirred at room temperature and a solution of K_2CO_3 (0.003 mol) in H_2O (2.5ml) was added, then the

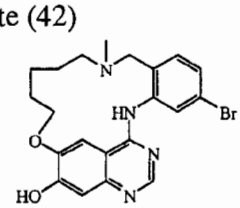
reaction mixture was heated to 60°C and stirred for 18 hours. The solvent was evaporated and H_2O (20ml) was added, then the mixture was neutralised with acetic acid and the formed precipitate was filtered off. The filtrate was concentrated under reduced pressure and the concentrate was extracted with CH_2Cl_2, filtered, then dried ($MgSO_4$) and the mixture was concentrated under reduced pressure, yielding 0.5g (70%) of intermediate (40).

g) Preparation of intermediate (41)



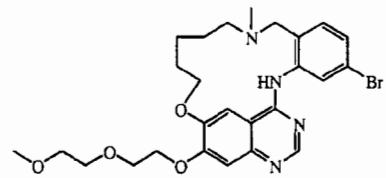
A solution of intermediate (40) (0.0011 mol) in THF (50ml) was stirred at room temperature and tributylphosphine (0.0016 mol) was added, then 1,1'-(azodicarbonyl)bispiperidine (0.0016 mol) was added and the reaction mixture was stirred for 2 hours. The solvent was evaporated until 1/3 of the initial volume. The resulting precipitate was filtered off and washed. The filtrate was evaporated and the residue was purified by high-performance liquid chromatography. The product fractions were collected and the organic solvent was evaporated. The aqueous concentrate was extracted 2 times with CH_2Cl_2 and the organic layer was dried ($MgSO_4$). The solvent was evaporated dry and the residue was dried (vacuum) at 50°C, yielding 0.004g (0.8 %) of intermediate (41).

h) Preparation of intermediate (42)



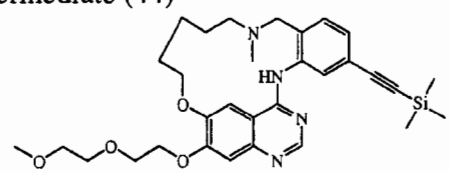
A 48% solution of hydrobromide in water (5.5ml) was added to a suspension of intermediate (41) (0.0058 mol) and potassium iodide (0.044 mol) in DMA (55ml), stirred at room temperature under N_2 flow. The reaction mixture was stirred for 2.5 hours at 130°C. The reaction mixture was poured onto ice water. The layers were separated. The aqueous layer was neutralised with NaOH (1N) and the resulting precipitate was filtered off, then dissolved in CH_2Cl_2, washed with water, separated and the organic phase was dried, filtered and the solvent evaporated under reduced pressure. The residue was stirred in water, filtered off, dissolved in THF and the solvent was evaporated (toluene was added and azeotroped on the rotary evaporator), yielding 1.58g (61%) of intermediate (42).

i) Preparation of intermediate (43)



Bis(1-methylethyl) ester diazenedicarboxylic acid (0.0158 mol) was added dropwise to a suspension of intermediate (42) (0.007895 mol), 2-(2-methoxyethoxy)ethanol (0.0631 mol) and triphenylphosphine (0.0158 mol) in THF (120ml), stirred at room temperature. The reaction mixture was stirred at room temperature for 20 minutes. The solvent was evaporated in vacuo. The residue was stirred for 10 minutes in CH_3CN at room temperature. The precipitate was filtered off, washed with CH_3CN and dried, yielding 3.37g (78%) of intermediate (43).

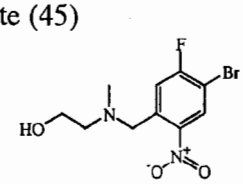
j) Preparation of intermediate (44)



Intermediate (43) (0.0009166 mol) was stirred in pyrrolidine (10ml). Dichlorobis(triphenylphosphine)palladium (0.00004583 mol) was added, followed by addition of copper iodide (catalytic quantity). The mixture was heated to 70°C. Ethynyltrimethylsilane (0.002292 mol) was added and the reaction mixture was stirred at 70°C for 4.75 hours. The reaction mixture was cooled to room temperature, filtered through dicalite and the filter residue was washed with CH_3OH. The filtrate was concentrated. The concentrate was redissolved in EtOAc, then partitioned between water and EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was redissolved in CH_3CN and treated with MP-TMT resin (0.002292 mol) to scavenge any residual Pd. The mixture was stirred slowly over the weekend. The mixture was filtered. The resin was washed with CH_3OH and the filtrate's solvent was evaporated, yielding 0.400g of intermediate (44).

Example A7

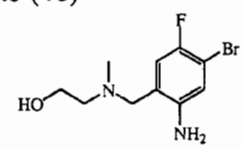
a) Preparation of intermediate (45)



A solution of 2-(methylamino)ethanol (0.077 mol) in CH_2Cl_2 (180ml) was stirred at room temperature. Tetrakis(2-methyl-2-propanolato)titanate(1-) (0.077 mol) was added, followed by triethylamine (0.077 mol). 4-Bromo-5-fluoro-2-nitrobenzaldehyde

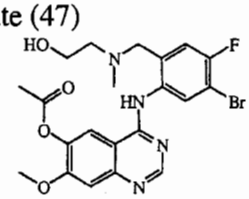
(0.077 mol) was added and the mixture was stirred for 90 minutes. $NaBH(OAc)_3$ (0.0847 mol) was added and the reaction mixture was stirred for 18 hours at room temperature. The mixture was poured into an aqueous $NaHCO_3$ solution. The precipitate was filtered off. The layers were separated. The organic phase was washed with water (2 x), dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1 to 99/2). The desired fractions were collected and the solvent was evaporated, yielding 18g of intermediate (45).

b) Preparation of intermediate (46)



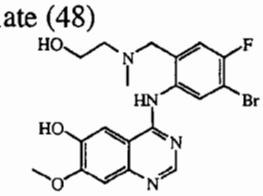
A mixture of intermediate (45) (0.059 mol) in EtOAc (250ml) was hydrogenated at room temperature and atmospheric pressure with 5% Pt/C (2 g) as a catalyst in the presence of vanadium oxide (0.5 g) and a 4% thiophene solution in DIPE (2ml). After uptake of H_2 (3 equiv), the catalyst was filtered off and the filtrate was evaporated, yielding intermediate (46) (quantitative yield).

c) Preparation of intermediate (47)



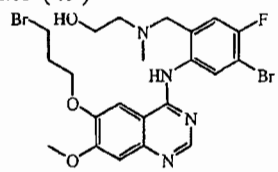
A mixture of intermediate (46) (0.0396 mol) and 4-chloro-7-methoxy-6-quinazolinol acetate ester (0.0396 mol) in 2-propanol (300ml) was stirred for 1 day at 75°C. More 4-chloro-7-methoxy-6-quinazolinol acetate ester (5 g) was added and the reaction mixture was stirred again for 1 day at 75°C. The solvent was evaporated under reduced pressure, yielding intermediate (47) (quantitative yield).

d) Preparation of intermediate (48)



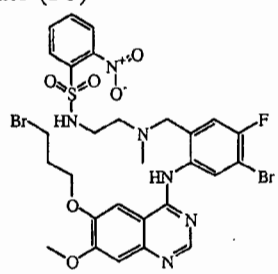
A mixture of intermediate (47) (0.0396 mol) in NH_3/CH_3OH (200ml) and CH_3OH (100ml) was stirred overnight at room temperature. The resulting precipitate was filtered off, washed and dried (vacuum, 60°C), yielding 15.7g of intermediate (48).

e) Preparation of intermediate (49)



A solution of intermediate (48) (0.0347 mol) in DMF (150ml) was stirred at room temperature and treated with K_2CO_3 (aq.) (0.16 mol). The reaction mixture was stirred for 45 minutes at room temperature. 1,3-Dibromopropane (0.31 mol) was added and the reaction mixture was stirred for 2 hours at room temperature. The mixture was poured onto ice/water, stirred for 10 minutes, and the resulting precipitate was filtered off, washed and dried (vacuum, 60°C). The solid was stirred in DIPE, filtered off, washed, then dried again in vacuo at 60°C, yielding 19.2g (97%) of intermediate (49).

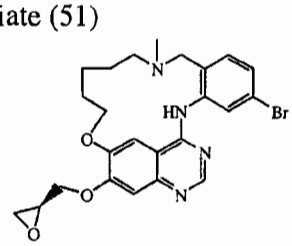
f) Preparation of intermediate (50)



A solution of intermediate (49) (0.033 mol), 2-nitrobenzenesulfonamide (0.10 mol) and triphenylphosphine (0.0495 mol) in THF (700ml) was stirred at room temperature. A solution of bis(1-methylethyl) ester diazenedicarboxylic acid (0.0495 mol) in THF (50ml) was added dropwise and the reaction mixture was stirred overnight. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography over silica gel. The product fractions were collected and the solvent was evaporated, yielding intermediate (50) (quantitative yield).

Example A8

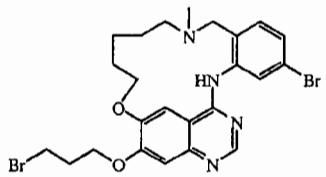
a) Preparation of intermediate (51)



DIAD (0.005 mol) was added dropwise to a mixture of intermediate (42) (0.0017 mol), (2R)-xiranemethanol (0.0105 mol) and triphenylphosphine (0.005 mol) in THF (30ml), stirred at room temperature for 5 hours. The precipitate was filtered off, washed with THF, and dried, yielding 0.545 g (64%) of intermediate (51) (R-configuration).

Example A9

a) Preparation of intermediate (52)

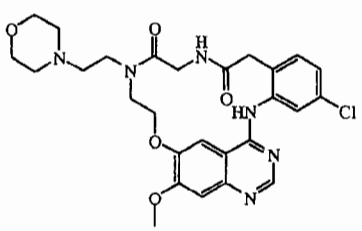


DIAD (0.0003 mol) was added dropwise to a solution of intermediate (42) (0.000138 mol), 3-bromo-1-propanol (0.00055 mol) and triphenylphosphine (0.0003 mol) in THF (2ml), stirred at room temperature. The reaction mixture was stirred for 1 hour at room temperature. The solvent was evaporated under a gentle flow of N_2, yielding intermediate (52) (quantitative yield).

B. Preparation of the compounds

Example B1

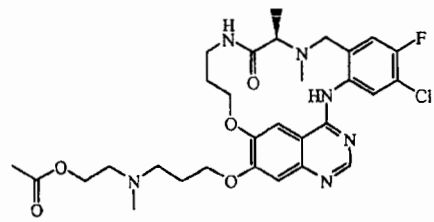
Preparation of compound (1)



HBTU (0.00195 mol) was added to a stirred solution of intermediate (6) (0.00069 mol) and DIPEA (0.00324 mol) in *N,N*-dimethylacetamide (250ml) at room temperature, then the reaction mixture was stirred for 3 hours and the solvent was co-evaporated with toluene under reduced pressure. The obtained residue was purified by reversed-phase high-performance liquid chromatography (eluent 1: NH_4OAc; eluent 2: NH_4HCO_3). The pure product fractions were collected and the solvent was evaporated under reduced pressure. The obtained residue (0.030 g) was crystallised from 2-propanol, then the resulting precipitate was filtered off and dried (vacuum), yielding 0.0165g of compound (1).

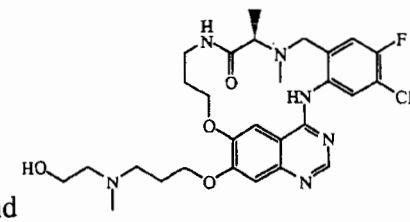
Example B2

Preparation of compound (2) and compound (3)



compound (2)

and

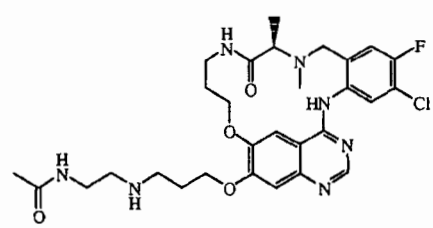


compound (3)

A mixture of intermediate (15) (0.0002 mol), 2-(methylamino)ethanol (0.0005 mol) and K_2CO_3 (aq.) (0.0002 mol) in CH_3CN (1.5ml) was stirred and refluxed overnight, then cooled to room temperature, poured into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness. The residue (0.16g) was purified by column chromatography over kromasil (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 99/1/0.05 to 88/12/1.2; 5μm). Two fractions were collected and the solvent was evaporated, yielding 0.009g (6%) of compound (3) (S-configuration) and 0.05g (31%) of compound (2) (S-configuration).

Example B3

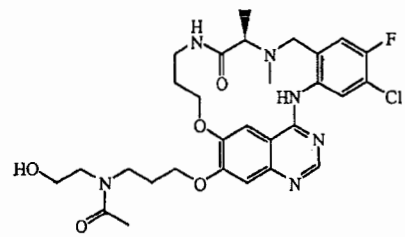
Preparation of compound (4)



A mixture of intermediate (15) (0.0002 mol), *N*-(2-aminoethyl)acetamide (0.0005 mol) and K_2CO_3 (aq.) (0.0002 mol) in CH_3CN (1.5ml) was stirred and refluxed overnight. *N*-(2-aminoethyl)acetamide and K_2CO_3 (aq.) were added again. The mixture was stirred and refluxed for 5 hours, then cooled to room temperature, poured into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness. The residue (0.146g) was purified by column chromatography over kromasil (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 99/1/0.05 to 75/25/1; 5μm). The pure fractions were collected and the solvent was evaporated. The residue (0.042g, 27%) was crystallized from diethyl ether. The precipitate was filtered off and dried, yielding 0.034g (22%) of compound (4) (S-configuration; M.P.: 112°C).

Example B4

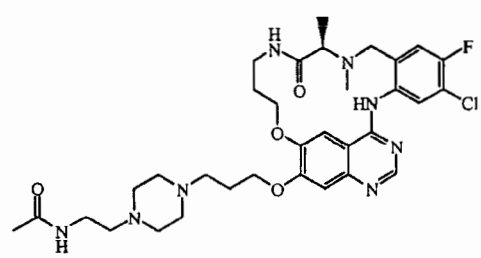
Preparation of compound (5)



A mixture of intermediate (15) (0.0002 mol), ethanolamine (0.0005 mol) and K_2CO_3 (aq.) (0.0002 mol) in CH_3CN (1.5ml) was stirred and refluxed overnight. CH_3OH was added. The mixture was stirred at room temperature for 18 hours, poured into H_2O and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness. The residue (0.12g) was purified by column chromatography over kromasil (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.4 to 86/4/1.4; 5μm). The pure fractions were collected and the solvent was evaporated, yielding 0.048g (33%) of compound (5) (S-configuration).

Example B5

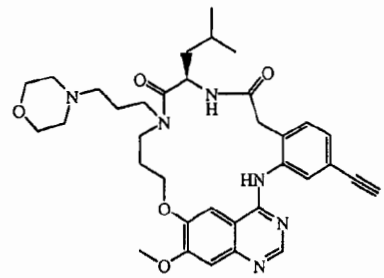
Preparation of compound (6)



A mixture of intermediate (17) (0.0001 mol), *N*-(2-chloroethyl)acetamide (0.0001 mol), K_2CO_3 (aq.) (0.0003 mol) and potassium iodide (0.004g) in ethanol (3ml) was stirred and refluxed for 3 days, then cooled to room temperature, poured into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness. The residue (0.097g) was purified by column chromatography over kromasil (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.5 to 90/10/0.5; 5μm). The pure fractions were collected and the solvent was evaporated. The residue (0.042g, 42%) was crystallized from CH_3CN. The precipitate was filtered off and dried, yielding 0.032g (32%) of compound (6) (S-configuration; M.P.: 136°C).

Example B6

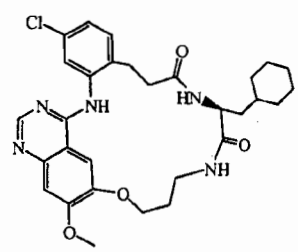
Preparation of compound (7)



A mixture of intermediate (26) (0.0006848 mol) in a saturated aqueous K_2CO_3 solution (60ml) and CH_3OH (60ml) was stirred for 30 minutes at room temperature. The solvent was evaporated and the residue was dissolved in CH_2Cl_2/H_2O. The layers were separated and the organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The crude residue was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1 till 95/5; column was stripped with $CH_2Cl_2/(CH_3OH/NH_3)$ 95/5). The desired fractions were purified again by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 100/0 to 97/3). The product fractions were collected and the solvent was evaporated. The residue was purified by high-performance liquid chromatography (ammonium acetate buffer). The product fractions were collected, the CH_3CN was evaporated and the aqueous layer was made alkaline (pH=10). The product was extracted with CH_2Cl_2. The separated organic layer was dried and the solvent was evaporated, yielding 0.419 g of compound (7) (S-configuration).

Example B7

Preparation of compound (8)

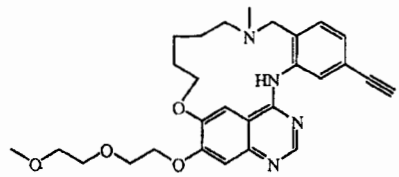


A solution of HBTU (excess) and DIPEA (3 equiv) in DMF (3ml) was stirred at room temperature. A solution of intermediate (34) (crude) in DMF (2ml) was added dropwise (Zymark). The resultant reaction mixture was stirred overnight at room temperature. The solvent was evaporated. The residue was purified by high-performance liquid

chromatography. The product fractions were collected and the solvent was evaporated, yielding 0.016g of compound (8) (S-configuration).

Example B8

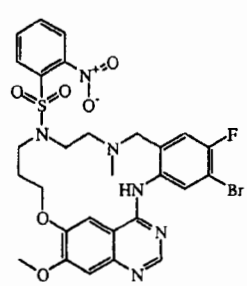
Preparation of compound (9)



Lithium hydroxide (0.340 g, 0.0081 mol) was added to a mixture of intermediate (44) (0.0006 mol) in CH_3OH (25ml) and H_2O (5ml), stirred at room temperature. The reaction mixture was stirred for one hour at 40°C. The mixture was concentrated under reduced pressure to one fifth of the initial volume. The concentrate was poured into water. The mixture was stirred for 30 minutes at room temperature. The precipitate was filtered off, stirred in THF (20ml) for one hour, then the precipitate was filtered off again. The solid was dissolved in THF/CH_3OH 1/1 (200ml). The whole was filtered and the filtrate was evaporated under reduced pressure. The residue was dried, then stirred for one hour in CH_3CN. The precipitate was filtered off and dried, yielding 0.142g (48%) of compound (9).

Example B9

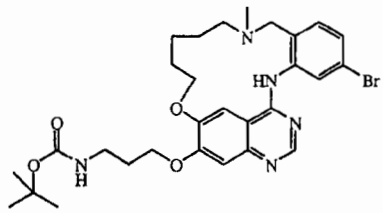
Preparation of compound (10)



To a stirred mixture of Cs_2CO_3 (0.018 mol), CH_3CN (100ml) and *N,N,N*-tributyl-1-butanaminium iodide (0.0072 mol) was added a solution of intermediate (50) (0.0036 mol) in CH_3CN (300ml) at 60°C. The reaction mixture was stirred for 4 hours at 60°C. The solvent was evaporated under reduced pressure. The residue was purified by high-performance liquid chromatography. The product fractions were collected and the solvent was evaporated, yielding 1.4g of compound (10).

Example B10

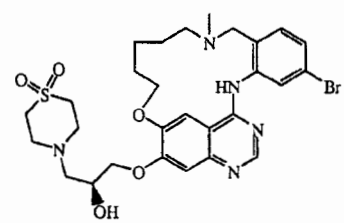
Preparation of compound (11)



A mixture of intermediate (42) (0.0017 mol), (3-hydroxypropyl)-1,1-dimethylethyl ester carbamic acid (0.0041 mol) and triphenylphosphine (0.0038 mol) in THF (20ml) was stirred at room temperature. DIAD (0.004 mol) was added dropwise and the reaction mixture was stirred for 1 hour at room temperature. The solvent was evaporated and the residue was stirred up in CH_3CN (50ml). The precipitate was filtered off, washed with CH_3CN and dried, yielding 0.815g (80%) of compound (11).

Example B11

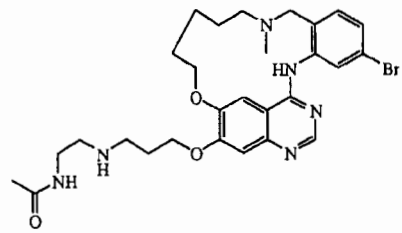
Preparation of compound (12)



A mixture of intermediate (51) (0.00032 mol) and 1,1-dioxidethiomorpholine (0.00185 mol) in 2-propanol (2ml) was stirred for 2 hours at 70°C. DMF (2ml) was added and the resultant reaction mixture was stirred for 16 hours at 70°C. The reaction mixture was cooled at room temperature slowly. The precipitate was filtered off and dried, yielding 0.108g (53%) of compound (12) (R-configuration).

Example B12

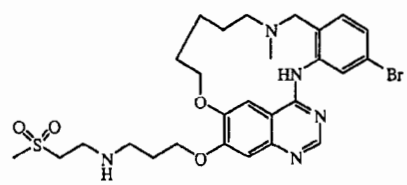
Preparation of compound (13)



Intermediate (52) (0.003190 mol) was stirred in CH_3CN (20ml). *N*-(2-aminoethyl)acetamide (2ml) was added and the resultant reaction mixture was stirred overnight at room temperature. K_2CO_3 (aq.) (0.009569 mol) was added and the reaction mixture was stirred and refluxed for 2 hours, then cooled to room temperature and the solvent was evaporated in vacuo. Water was added to the residue and this mixture was stirred for 30 minutes at room temperature. The yellow precipitate was filtered off and dried. This fraction was purified by flash column chromatography over a Biotage cartridge (eluent: CH_2Cl_2/(CH_3OH/NH_3) 95/5 up to 80/20). The product fractions were collected and the solvent was evaporated, yielding 0.94g of compound (13).

Example B13

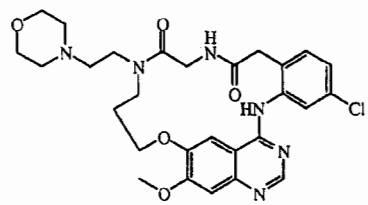
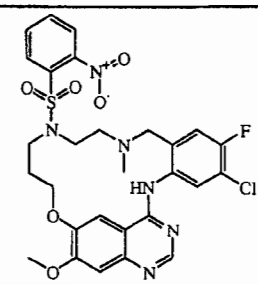
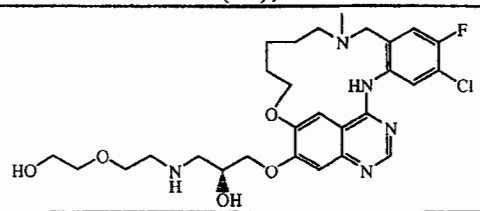
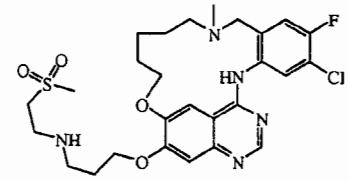
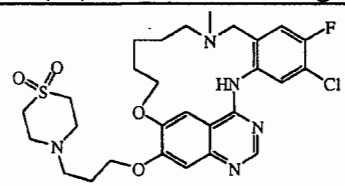
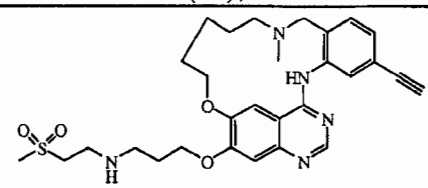
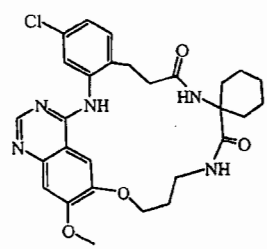
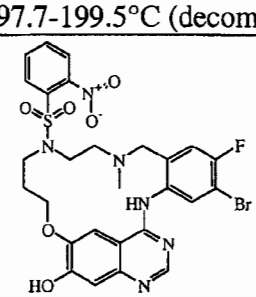
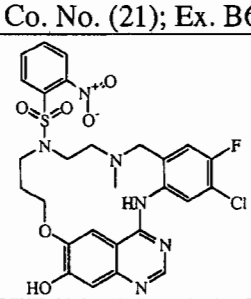
Preparation of compound (14)



Intermediate (52) (0.003544 mol) was stirred in CH_3CN (20ml). 2-(Methylsulfonyl)ethanamine hydrochloride (0.007088 mol) was added. K_2CO_3 (aq.) (0.0106 mol) was added and the reaction mixture was stirred and refluxed overnight, then cooled to room temperature and the solvent was evaporated in vacuo. Water was added to the residue and this mixture was stirred for 10 minutes at room temperature. The yellow precipitate was filtered off and dried. This fraction was purified by flash column chromatography over a Biotage cartridge (eluent: CH_2Cl_2/(CH_3OH/NH_3) from 100/0 to 94/6). The product fractions were collected and the solvent was evaporated, yielding 1.24g (58%) of compound (14).

Table F-1 lists the compounds that were prepared according to one of the above Examples. The following abbreviations were used in the tables : M.P. stands for the melting point.

Table F-1

	
Co. No. (15); Ex. B1	Co. No. (16); Ex. B9
	
Co. No. (17); Ex. B11; R-configuration	Co. No. (18); Ex. B12
	
Co. No. (19); Ex. B12	Co. No. (20); Ex. B13; M.P.: 197.7-199.5°C (decomposition)
	
Co. No. (21); Ex. B6	Co. No. (22); Ex. B9
	
Co. No. (23); Ex. B9	

Compound identification

LCMS-methods:

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.

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 ammonium acetate + 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.

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.

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.

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 ammonium acetate + 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 % 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:

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 ammonium acetate; 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.

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

Comp. No.	Rt	MW(MH+)	LC/GC/MS Method
Int. 35	3.84	317	1
Int. 41	1.24	457	1
Int. 40	6.01	475	1
Int. 1	3.99	271	1
Int. 2	5.31	487	1
Int. 22	10.12	652	1
Int. 25	9.62	684	1
10	6.24	675	1
16	6.21	631	1
22	5.92	661	1
23	5.89	617	1
17	8.48	578	1
Int. 39	6.32	559	1
Int. 37	6.47	373	1
Int. 36	5.53	331	1
Int. 3	4.62	445	1
Int. 4	5.63	551	1
Int. 5	4.39	601	1
Int. 23	8.26	729	1
Int. 21	1	531	2
Int. 43	1.2	545	2
Int. 42	1.16	443	2
Int. 44	1.29	563	2
Int. 49	1.12	573	2
Int. 47	1.03	493	2
11	1.27	600	2
12	1.13	634	2
Int. 51	1.2	499	2
14	1.18	606	2
Int. 45	1.13	307	2
19	1.17	592	2

18	1.17	580	2
Int. 20	1.05	575	2
Int. 52	1.27	565	2
Int. 48	0.98	451	2
20	7.41	551	3
8	9.24	566	3
21	8.11	538	3
13	6.43	585	4
Int. 12	6.57	490	5
Int. 13	8.62	474	5
Int. 10	4.95	449	5
Int. 15	6.32	536	5
Int. 17	4.88	586	5

C. Pharmacological examples

C1 Kinase profiling

The *in vitro* inhibition of a panel of kinases was assessed using the glass-fiber 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 (^{33}P) radiolabeled ATP. (^{33}P) Phosporylation of the substrate is 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 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_3VO_4, 0.1% β-mercaptoethanol, 1 mg/ml BSA	Blk, Fyn, Lck, 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, Bmx, EGFR, Fes, Fgr, Fms, Flt1, CDK5/p35, CDK6/cyclinD3, ErbB4, cSRC, Ret, Yes, Hck

All substrates are dissolved and diluted to working stocks in de-ionised water.

Abl human

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-^{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 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.

Blk mouse

In a final reaction volume of 25 µl, Blk (m) (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 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.

Bmx human

In a final reaction volume of 25 µl, Bmx (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 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.

CDK5/p35 human

In a final reaction volume of 25 µl, CDK5/p35 human (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.1 mg/ml histone H1, 10 mM MgAcetate and [γ-^{33}P-ATP] (specific activity approx. 500cpm/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.

CDK6/cyclinD3 human

In a final reaction volume of 25 µl, CDK6/cyclinD3 human (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.1 mg/ml histone H1, 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 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.

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-^{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 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.

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 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 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.

ErbB4 human

In a final reaction volume of 25 µl, 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

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 prior to drying and scintillation counting.

Fgr human

In a final reaction volume of 25 μl, Fgr human (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 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.

Fyn human

In a final reaction volume of 25 μl, Fyn human (5-10 mU) is incubated with 50 mM Tris pH 7.5, 0.1 mM EGTA, 0.1 mM Na_3VO_4, 250 μM KVEKIGEGTYGVVYK (Cdc2 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 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.

Lck human

In a final reaction volume of 25 μl, Lck (h) (5-10 mU) is incubated with 50 mM Tris pH 7.5, 0.1 mM EGTA, 0.1 mM Na3VO4, 250 μM KVEKIGEGTYGVVYK (Cdc2 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 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.

Lyn human

In a final reaction volume of 25 µl, 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-^{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 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.

Ret human

In a final reaction volume of 25 µl, Ret human (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 µM 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 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.

Yes human

In a final reaction volume of 25 µl, 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-^{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 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.

Flt1 human

In a final reaction volume of 25 µl, Flt1 human (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 250 µM 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 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.

Hck human

In a final reaction volume of 25 µl, Hck human (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-^{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 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.

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.

Compound No	Abl	CDK5/p35	CDK6/cyclinD3	cSRC	EGFR	Fgr
Int. 43	3		1	4	4	2
1				3	4	
15	4	1		2	4	
Int. 25	1			2	4	
8	1			4	4	
11				3	4	1
12				4	4	3
13				4	4	4
14				4	4	3
20				4		4
19				4	4	3
2				4	4	1
4				4	4	
Int. 16				4	4	1
5				4	4	1
6	4			4	4	
17	4			4	4	
18	4			4	4	

Compound No	Fyn	Lck	Lyn	Ret	Yes	Flt1
43	4	4	4	4	4	3
1		1	2		2	
15	2	2	3	1	3	1
Int. 25	2	3	3	2	4	1
8	3	4		4	4	
11	3		2	4	4	2
12	4	4	4	4	4	3
13		4	4	4	4	4
14		4	4	4	4	4
20		4	4	4	4	4
19	4	4		4	4	4
2	4	4		4	4	2
4	3	4		4	4	2
Int. 16	4	4	4	4		3
5	3	3	4	3	4	2
6	4	4	4		4	
17	4	4	4		4	
18	4	4	4		4	

Compound No	Blk	Bmx	ErbB4
43	3	-	1
1	2		
15	2		1
Int. 25	2		2
8			3
11	2	1	1
12	4	2	3
13	4	3	4
14	4	2	4
20	4	3	4
19	4	3	3
2	4	2	2
4	4	2	2
Int. 16	4	2	1
5	4	2	1
6		2	3
17		3	4
18		2	4

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.

"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

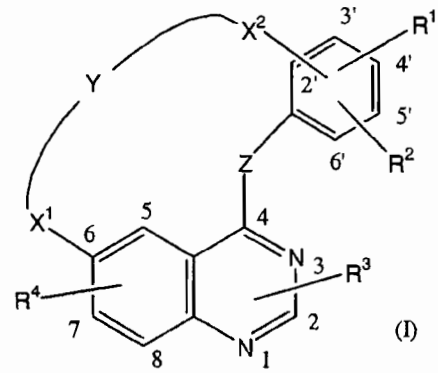
A mixture of A.I. (100 g), lactose (570 g) and starch (200 g) was mixed well and thereafter humidified with a solution of sodium dodecyl sulfate (5 g) and polyvinyl-pyrrolidone (10 g) in about 200ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added microcrystalline 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

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

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

Z represents NH;

Y represents -C_{3-9}alkyl-, -C_{2-9}alkenyl-, -C_{1-5}alkyl-oxy-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-6}alkyl-NH-CO-, -NH-CO-C_{1-6}alkyl-, -CO-C_{1-7}alkyl-, -C_{1-7}alkyl-CO-, C_{1-6}alkyl-CO-C_{1-6}alkyl, -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-, -C_{1-2}alkyl-CO-NH-$CR^{18}R^{19}$-CO-, -C_{1-2}alkyl-CO-NR^{20}-C_{1-3}alkyl-CO-, -C_{1-2}alkyl-NR^{21}-CH_2-CO-NH-C_{1-3}alkyl-, -NR^{22}-CO-C_{1-3}alkyl-NH-, -C_{1-3}alkyl-NH-CO-Het^{20}-, C_{1-2}alkyl-CO-Het^{21}-CO-, or -Het^{22}-CH_2-CO-NH-C_{1-3}alkyl-;

X^1 represents O, -O-C_{1-2}alkyl-, -O-N=CH-, NR^{11} or -NR^{11}-C_{1-2}alkyl-;

X^2 represents a direct bond, C_{1-2}alkyl, O, -O-C_{1-2}alkyl-, CO, -CO-C_{1-2}alkyl-, -O-N=CH-, NR^{12} or NR^{12}-C_{1-2}alkyl-;

R^1 represents hydrogen, cyano, halo or hydroxy, preferably halo;

R^2 represents hydrogen, cyano, halo, hydroxy, hydroxycarbonyl-, C_{1-4}alkyloxycarbonyl-, Het^{16}-carbonyl-, C_{1-4}alkyl-, C_{2-6}alkynyl-, Ar^5, Het^1 or dihydroxyborane;

R^3 represents hydrogen, cyano, halo, hydroxy, formyl, C_{1-6}alkoxy-, C_{1-6}alkyl-, C_{1-6}alkoxy- substituted with halo, or R^3 represents C_{1-4}alkyl substituted with one or where possible two or more substituents selected from hydroxy or halo;

R^4 represents Ar^4-C_{1-4}alkyloxy-, C_{1-4}alkyloxy- or R^4 represents C_{1-4}alkyloxy substituted with one or where possible two or more substituents selected from hydroxy-, halo, C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy-, $NR^{37}R^{38}$-carbonyloxy-, Het^5-carbonyloxy-, NR^7R^8, NR^9R^{10}-carbonyl-, Het^3-carbonyl-, Het^{13}-oxy- or Het^2-;

R^7 represents hydrogen, hydroxy-C_{1-4}alkyl- or C_{1-4}alkyl;

R^8 represents C_{3-6}cycloalkyl; Het^6-carbonyl-; Het^7-aminocarbonyl-; Het^8; Het^9-oxycarbonyl-; Het^{10}-sulfonyl-; C_{1-4}alkyloxycarbonyl; mono- or di(C_{1-4}alkyl)aminocarbonyl-; mono- or di(C_{1-4}alkyl)aminocarbonyl substituted with C_{1-4}alkylsulfonyl-; or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from C_{1-4}alkylsulfonyl, hydroxy- and C_{1-4}alkyloxy-; or

R^8 represents C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, $NR^{25}R^{26}$, aminocarbonyloxy-, C_{1-4}alkylcarbonyloxy-, aminocarbonyl-, hydroxy-C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy-, and Het^{11};

R^9 represents hydrogen or C_{1-4}alkyl-;

R^{10} represents Het^4 or C_{1-4}alkyl- substituted with C_{1-4}alkylsulfonyl-, ;

R^{11} represents hydrogen, C_{1-4}alkyl- or C_{1-4}alkyl-oxy-carbonyl-;

R^{12} represents hydrogen, C_{1-4}alkyl-, C_{1-6}alkyloxycarbonyl- or C_{1-6}alkyloxycarbonyl- substituted with phenyl;

R^{13} represents hydrogen, Het^{14}-C_{1-4}alkyl, C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl;

R^{14} and R^{15} are each independently selected from hydrogen, C_{1-4}alkyl, Het^{15}-C_{1-4}alkyl- or C_{1-4}alkyloxyC_{1-4}alkyl-;

R^{16} and R^{17} each independently represents hydrogen, C_{1-4}alkyl or C_{1-4}alkyl substituted with hydroxy-, C_{3-6}cycloalkyl or phenyl; or R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{18} represents hydrogen or C_{1-4}alkyl optionally substituted with hydroxy or phenyl;

R^{19} represents hydrogen or C_{1-4}alkyl;

R^{20} represents hydrogen or C_{1-4}alkyl;

R^{21} represents hydrogen, C_{1-4}alkyl, Het^{23}-C_{1-4}alkylcarbonyl- or R^{21} represents mono-or di(C_{1-4}alkyl)amino-C_{1-4}alkyl-carbonyl- optionally substituted with hydroxy, pyrimidinyl, dimethylamine or C_{1-4}alkyloxy;

R^{22} represents hydrogen or C_{1-4}alkyl optionally substituted with hydroxy or C_{1-4}alkyloxy;

R^{23} represents C_{1-4}alkyl optionally substituted with hydroxy-, C_{1-4}alkyloxy- or Het^{25}; R^{23} may also represent hydrogen when R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{25} and R^{26} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{27} and R^{28} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-; or for those compounds of formula (I) wherein Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl pyrrolidinyl or thiomorpholinyl substituted with $NR^{27}R^{28}$-C_{1-4}alkyl said R^{27} and R^{28} each independently represent C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{29} and R^{30} each independently represent hydrogen, aminosulfonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{31}R^{32}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

R^{31} and R^{32} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{33} represents hydrogen or C_{1-4}alkyl;

R^{34} represents C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{35} represents hydrogen or C_{1-4}alkyl;

R^{36} represents C_{1-4}alkylsulfonyl-, aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminocarbonyl-, C_{1-4}alkylcarbonyl-, C_{1-4}alkyloxycarbonyl- or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{37} and R^{38} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl-, Het^{12} or C_{1-4}alkyl substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy- and C_{1-4}alkyloxy-;

R^{39} and R^{40} each independently represent aminosulfonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- substituted with one or more substituents selected from $NR^{31}R^{32}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

Het^1 represents thiazolyl or 2-bora-1,3-dioxolanyl wherein said Het^1 is optionally substituted with one or where possible two, three, four or more substituents selected from 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-;

Het^2 represents a heterocycle selected from tetrahydropyranyl, tetrahydrofuranyl, furanyl, 1,1-dioxothiomorpholinyl, piperazininonyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, azetidinyl or 2-azetidinonyl wherein said Het^2 is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino, $NR^{29}R^{30}$, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{1-4}alkylsulfonyl or C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-, or C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or

Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, thiomorpholinyl or 1,1-dioxothiomorpholinyl wherein said Het^2 is optionally substituted with one or where possible two or more substituents selected from C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-, or C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or

C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

Het^3 represents a heterocycle selected from tetrahydropyranyl, tetrahydrofuranyl, furanyl, 1,1-dioxothiomorpholinyl, piperazininonyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, azetidinyl or 2-azetidinonyl wherein said Het^3 is optionally substituted with one or where possible two or more substituents hydroxy-, amino, C_{1-4}alkyl-, C_{3-6}cycloalkyl-C_{1-4}alkyl-, aminosulfonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, amino-C_{1-4}alkyl-, Mono- or di(C_{1-4}alkyl)amino-C_{1-4}alkyl, $NR^{35}R^{36}$, C_{1-4}alkyl-sulfonyl-C_{1-4}alkyl- or C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy- or hydroxy; or

Het^3 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, furanyl or pyrrolidinyl wherein said Het^3 is substituted with one or where possible two or more substituents selected from $NR^{35}R^{36}$, C_{1-4}alkyl-sulfonyl-C_{1-4}alkyl- or C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy- or hydroxy;

Het^4 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, furanyl, pyrazolyl, dioxolanyl, thiazolyl, oxazolyl, imidazolyl, isoxazolyl, oxadiazolyl, pyridinyl or pyrrolidinyl wherein said Het^4 is substituted with one or where possible two or more substituents selected from C_{1-4}alkyl-sulfonyl-C_{1-4}alkyl-, C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy- or hydroxy;

Het^5 represents a heterocycle selected from furanyl, piperazinyl, 1,1-dioxothiomorpholinyl, piperazininonyl, piperidinyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, morpholinyl or pyrrolidinyl wherein said Het^5 is optionally substituted with hydroxy, amino, mono- or di(C_{1-4}alkyl)-amino-, C_{1-4}alkyl,

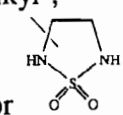
Het^6 and Het^7 each independently represents a heterocycle selected from piperazinyl, piperidinyl or pyrrolidinyl wherein said heterocycles are optionally substituted with one or more substituents selected from hydroxy-, amino, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxy-C_{1-4}alkyl- and C_{1-4}alkyl-;

Het^8 represents a heterocycle selected from tetrahydropyranyl, tetrahydrofuranyl, 1,1-dioxothiomorpholinyl, piperazininonyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, azetidinyl or 2-azetidinonyl wherein said Het^8 is optionally substituted with aminosulfonyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or C_{1-4}alkyl- optionally substituted with one or more substituents selected from amino, mono- or di(C_{1-4}alkyl)amino-, $NR^{33}R^{34}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or

C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or
C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or

Het^8 represents a heterocycle selected from furanyl, piperidinyl or piperazinyl wherein said Het^8 is substituted with aminocarbonyl,
mono- or di(C_{1-4}alkyl)aminocarbonyl-, mono- or di(C_{1-4}alkyl)aminosulfonyl-, or
C_{1-4}alkyl- substituted with one or more substituents selected from $NR^{33}R^{34}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, hydroxy-, C_{1-4}alkyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-, or
C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-, or
C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;

Het^9 and Het^{10} each independently represents a heterocycle selected from piperazinyl, piperidinyl or pyrrolidinyl wherein said heterocycles are optionally substituted with one or more substituents selected from hydroxy-, amino, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxy-C_{1-4}alkyl- and C_{1-4}alkyl-;

Het^{11} represents 2-imidazolidinonyl- or ;

Het^{12} represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^{12} is optionally substituted with one or where possible two or more substituents selected from hydroxy, amino or C_{1-4}alkyl-;

Het^{13} represents a heterocycle selected from furanyl, piperazinyl, 1,1-dioxothiomorpholinyl, piperazininonyl, piperidinyl, tetrahydro-1,1-dioxido-2H-thiopyranyl, piperidinonyl, morpholinyl, piperazinyl or pyrrolidinyl;

Het^{14} and Het^{15} each independently represent a heterocycle selected from morpholinyl, piperazinyl, piperidinyl or pyrrolidinyl wherein said Het^{14} and Het^{15} are optionally substituted with one or where possible two or more substituents selected from hydroxy, amino or C_{1-4}alkyl;

Het^{16} represents a heterocycle selected from piperidinyl or pyrrolidinyl;

Het^{20} represents pyrrolidinyl, 2-pyrrolidinonyl, piperidinyl or hydroxy-pyrrolidinyl, preferably pyrrolidinyl or hydroxy-pyrrolidinyl;

Het^{21} represents pyrrolidinyl or hydroxy-pyrrolidinyl;

Het^{22} represents pyrrolidinyl, piperazinyl or piperidinyl;

Het^{23} and Het^{25} each independently represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl wherein said Het^{23} is optionally substituted

with one or where possible two or more substituents selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, hydroxy-C_{1-4}alkyl-, C_{1-4}alkyloxyC_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl-;

Het^{24} represents morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl;

Ar^4, Ar^5 or Ar^6 each independently represent phenyl optionally substituted with nitro, cyano, C_{1-4}alkylsulfonyl-, C_{1-4}alkylsulfonylamino-, aminosulfonylamino-, hydroxy-C_{1-4}alkyl, aminosulfonyl-, hydroxy-, C_{1-4}alkyloxy- or C_{1-4}alkyl, preferably Ar^4 or Ar^5 each independently represent phenyl optionally substituted with cyano;

further characterised in that either

Y represents -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-;

Het^1 represents 2-bora-1,3-dioxolanyl optionally substituted with one or where possible two, three, four or more substituents selected from 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-;

R^{13} represents C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl; or

R^4 represents C_{1-4}alkyloxy substituted with at least one substituent selected from C_{1-4}alkyloxy-C_{1-4}alkyloxy-, $NR^{37}R^{38}$-carbonyloxy-, Het^5-carbonyloxy-, NR^7R^8, NR^9R^{10}-carbonyl-, Het^3-carbonyl-, Het^{13}-oxy- or Het^2-; wherein

R^8 represents Het^7-aminocarbonyl-; Het^9-oxycarbonyl-; Het^{10}-sulfonyl-; C_{1-4}alkyloxycarbonyl; mono- or di(C_{1-4}alkyl)aminocarbonyl-; mono- or di(C_{1-4}alkyl)aminocarbonyl substituted with C_{1-4}alkylsulfonyl-; or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from C_{1-4}alkylsulfonyl, hydroxy- and C_{1-4}alkyloxy-; or

R^8 represents C_{1-4}alkyl substituted with one or more substituents selected from hydroxy C_{1-4}alkylsulfonyl-, $NR^{25}R^{26}$, aminocarbonyloxy-, C_{1-4}alkylcarbonyloxy-, aminocarbonyl-, C_{1-4}alkyloxy-C_{1-4}alkyloxy-, and Het^{11};

Het^{13} represents C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl; in particular morpholinyl-C_{1-4}alkyl; and

Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl or thiomorpholinyl said Het^2 substituted with one or where possible two or more substituents selected from C_{1-4}alkyl- substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and

mono- or di(C_{1-4}alkyl)aminocarbonyl-; or
C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-; or
C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-;
or Het^2 represents 1,1-dioxothiomorpholinyl optionally substituted with C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-; or
C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-; or
C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-.

2. A compound according to claim 1 wherein;

Z represents NH;

Y represents -C_{3-9}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-6}alkyl-CO-NH-, -C_{1-6}alkyl-NH-CO-, -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-, -C_{1-2}alkyl-NR^{21}-CH_2-CO-NH-C_{1-3}alkyl or C_{1-3}alkyl-NH-CO-Het^{20}-;

X^1 represents a direct bond, O, -O-C_{1-2}alkyl-, NR^{11}, or -NR^{11}-C_{1-2}alkyl-;

X^2 represents a direct bond, -C_{1-2}alkyl-, CO-C_{1-2}alkyl or NR^{12}-C_{1-2}alkyl-;

R^1 represents hydrogen, cyano, halo or hydroxy;

R^2 represents hydrogen, halo, cyano, C_{2-6}alkynyl, hydroxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl- or Het^1;

R^3 represents hydrogen, cyano, halo, hydroxy, formyl, C_{1-6}alkyloxy or C_{1-6}alkyloxy- substituted with halo;

R^4 represents Ar^4-C_{1-4}alkyloxy, C_{1-4}alkyloxy-, or C_{1-4}alkyloxy- substituted with one or where possible two or more substituents selected from hydroxy, C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy, NR^7R^8 or Het^2;

R^7 represents hydrogen, hydroxyC_{1-4}alkyl- or C_{1-4}alkyl;

R^8 represents C_{1-4}alkyloxycarbonyl or C_{1-4}alkyl- substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, C_{1-4}alkylcarbonyloxy or $NR^{25}R^{26}$; in particular R^8 represents C_{1-4}alkyl- substituted with one or more substituents selected from C_{1-4}alkylsulfonyl- or $NR^{25}R^{26}$;

R^{11} represents hydrogen, C_{1-4}alkyloxycarbonyl or C_{1-4}alkyl;

R^{12} represents hydrogen or C_{1-4}alkyl;

R^{13} represents C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl;

R^{14} and R^{15} each independently represent hydrogen or C_{1-4}alkyl;

R^{16} and R^{17} each independently represent hydrogen or C_{1-4}alkyl optionally substituted with C_{3-6}cycloalkyl or R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{21} represents hydrogen or C_{1-4}alkyloxycarbonyl;

R^{23} represents C_{1-4}alkyl optionally substituted with hydroxy-, C_{1-4}alkyloxy- or Het^{25}; R^{23} may also represent hydrogen when R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{25} and R^{26} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl, C_{1-4}alkyloxycarbonyl or C_{1-4}alkylcarbonyl;

R^{27} and R^{28} each independently represent hydrogen, C_{1-4}alkyl, C_{1-4}alkylsulfonyl, C_{1-4}alkyloxycarbonyl or C_{1-4}alkylcarbonyl;

Het^1 represents 2-bora-1,3-dioxolanyl- optionally substituted with one or where possible two, three, four or more substituents selected from amino, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl-, phenyl, phenyl-C_{1-4}alkyl, C_{1-4}alkyloxyC_{1-4}alkyl-, mono- or di(C_{1-4}alkyl)amino- or aminocarbonyl-;

Het^2 represents 1,1-dioxothiomorpholinyl optionally substituted with C_{1-4}alkyloxycarbonyl or C_{1-4}alkyl-$NR^{27}R^{28}$; or Het^2 represents piperidinyl or piperazinyl substituted with C_{1-4}alkyloxycarbonyl or -C_{1-4}alkyl-$NR^{27}R^{28}$;

Het^{20} represents pyrrolidinyl, 2-pyrrolidinonyl, piperidinyl or hydroxy-pyrrolidinyl;

Het^{25} represents a heterocycle selected from morpholinyl or piperazinyl wherein said heterocycle is optionally substituted with C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyloxy-C_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl; or

Ar^4, Ar^5 or Ar^6 each independently represents phenyl optionally substituted with nitro, cyano, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkyl or C_{1-4}alkyloxy;

further characterised in that either

Y represents $-C_{1-2}$alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-; or

R^4 represents C_{1-4}alkyloxy substituted with at least one substituent selected from C_{1-4}alkyloxy-C_{1-4}alkyloxy-, NR^7R^8 or Het^2.

3. A compound according to claims 1 or 2 wherein;

Z represents NH;

Y represents -C_{3-9}alkyl-, -C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-, -C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-, -C_{1-6}alkyl-CO-NH-, -C_{1-6}alkyl-NH-CO-, -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-, -C_{1-2}alkyl-NR^{21}-CH_2-CO-NH-C_{1-3}alkyl or C_{1-3}alkyl-NH-CO-Het^{20}-;

X^1 represents a direct bond, O, -O-C_{1-2}alkyl-, NR^{11}, or -NR^{11}-C_{1-2}alkyl-;

X^2 represents a direct bond, -C_{1-2}alkyl-, CO-C_{1-2}alkyl or NR^{12}-C_{1-2}alkyl-;

R^1 represents hydrogen or halo;

R^2 represents hydrogen, halo, C_{2-6}alkynyl, cyano or Het^1;

R^3 represents hydrogen;

R^4 represents Ar^4-C_{1-4}alkyloxy, C_{1-4}alkyloxy-, or C_{1-4}alkyloxy- substituted with one or where possible two or more substituents selected from hydroxy, C_{1-4}alkyloxy-, C_{1-4}alkyloxy-C_{1-4}alkyloxy, NR^7R^8 or Het^2;

R^7 represents hydrogen or C_{1-4}alkyl;

R^8 represents C_{1-4}alkyloxycarbonyl or C_{1-4}alkyl- substituted with one or more substituents selected from C_{1-4}alkylsulfonyl-, hydroxy, C_{1-4}alkylcarbonyloxy or $NR^{25}R^{26}$;

R^{11} represents hydrogen or C_{1-4}alkyl;

R^{12} represents hydrogen or C_{1-4}alkyl;

R^{13} represents Ar^6-sulfonyl or C_{1-6}alkyloxycarbonyl optionally substituted with phenyl;

R^{14} and R^{15} represent hydrogen;

R^{16} and R^{17} each independently represent hydrogen or C_{1-4}alkyl optionally substituted with C_{3-6}cycloalkyl or R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{21} represents hydrogen or C_{1-4}alkyloxycarbonyl;

R^{23} represents C_{1-4}alkyl optionally substituted with hydroxy-, C_{1-4}alkyloxy- or Het^{25}; R^{23} may also represent hydrogen when R^{16} and R^{17} taken together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl;

R^{25} and R^{26} each independently represent hydrogen or C_{1-4}alkylcarbonyl;

R^{27} and R^{28} each independently represent hydrogen or C_{1-4}alkylcarbonyl;

Het^1 represents 2-bora-1,3-dioxolanyl-;

Het^2 represents 1,1-dioxothiomorpholinyl, piperidinyl or piperazinyl wherein said Het^2 is optionally substituted with C_{1-4}alkyloxycarbonyl or -C_{1-4}alkyl-$NR^{27}R^{28}$;

Het^{20} represents pyrrolidinyl;

Het^{25} represents a heterocycle selected from morpholinyl or piperazinyl wherein said heterocycle is optionally substituted with C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyloxy-C_{1-4}alkyl or polyhydroxy-C_{1-4}alkyl;

Ar^4 represents phenyl;

Ar^5 represents phenyl; or

Ar^6 represents phenyl optionally substituted with nitro;
further characterised in that either
Y represents $-C_{1-2}alkyl-NR^{23}-CO-CR^{16}R^{17}-NH-$; or
R^4 represents $C_{1-4}alkyloxy$ substituted with at least one substituent selected from $C_{1-4}alkyloxy-C_{1-4}alkyloxy-$, NR^7R^8 or Het^2; in particular $C_{1-4}alkyloxy$ substituted with $C_{1-4}alkyloxy-C_{1-4}alkyloxy-$ or NR^7R^8.

4. A compound according to any one of claims 1 to 3 wherein;
Z represents NH;
Y represents $-C_{3-9}alkyl-$, $-C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl-$, $-C_{1-5}alkyl-NR^{14}-CO-C_{1-5}alkyl-$, $-C_{1-2}alkyl-NR^{21}-H_2-CO-NH-C_{1-3}alkyl-$ or $-C_{1-2}alkyl-NR^{23}-CO-CR^{16}R^{17}-NH-$;
X^1 represents O or $-O-C_{1-2}alkyl-$;
X^2 represents a direct bond, $C_{1-2}alkyl$, $-CO-C_{1-2}alkyl$ or $NR^{12}-C_{1-2}alkyl$;
R^1 represents hydrogen or halo; in particular R^1 represents hydrogen;
R^2 represents halo, acetylene or Het^1; in particular R^2 represents halo or Het^1;
R^3 represents hydrogen;
R^4 represents $Ar^4-C_{1-4}alkyloxy-$, $C_{1-4}alkyloxy-$ or $C_{1-4}alkyloxy$ substituted with one or where possible two or more substituents selected from Het^2, NR^7R^8, hydroxy and $C_{1-4}alkyloxy-C_{1-4}alkyloxy-$;
R^7 represents hydrogen or $C_{1-4}alkyl$;
R^8 represents $C_{1-4}alkyl$ substituted with $NR^{25}R^{26}$ or $C_{1-4}alkylsulfonyl$;
R^{12} represents hydrogen or $C_{1-4}alkyl-$;
R^{13} represents Ar^6-sulfonyl or $C_{1-6}alkyloxycarbonyl$ optionally substituted with phenyl;
R^{16} and R^{17} represents hydrogen, $C_{1-4}alkyl$ or R^{16} and R^{17} taken together with the carbon atom to which they are attached from a $C_{3-6}cycloalkyl$;
R^{23} represents hydrogen or $C_{1-4}alkyl$;
R^{25} and R^{26} each independently represent hydrogen or $C_{1-4}alkylcarbonyl$;
R^{27} and R^{28} each independently represent hydrogen or $C_{1-4}alkylcarbonyl$;
Het^1 represents 2-bora-1,3-dioxolanyl;
Het^2 represents piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or 1,1-dioxothiomorpholinyl wherein said Het^2 is optionally substituted with $C_{1-4}alkyloxycarbonyl$ or $NR^{27}R^{28}-C_{1-4}alkyl$;
Ar^4 represents phenyl;
Ar^5 represents phenyl; or
Ar^6 represents phenyl optionally substituted with nitro.

5. A compound according to any one of claims 1 to 3 wherein;
Z represents NH;
Y represents -C_{3-9}alkyl-,-C_{1-5}alkyl-NR^{13}-C_{1-5}alkyl- or
–C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH-;
X^1 represents O; X^2 represents a direct bond or NR^{12}-C_{1-2}alkyl-;
R^1 represents hydrogen; R^2 represents halo or Het^1; R^3 represents hydrogen;
R^4 represents Ar^4-C_{1-4}alkyloxy-, C_{1-4}alkyloxy- or C_{1-4}alkyloxy substituted with C_{1-4}alkyloxy-C_{1-4}alkyloxy-;
R^{12} represents hydrogen or C_{1-4}alkyl-;
R^{13} represents Ar^6-sulfonyl or C_{1-6}alkyloxycarbonyl optionally substituted with phenyl;
R^{16} and R^{17} taken together with the carbon atom to which they are attached from a C_{3-6}cycloalkyl;
R^{23} represents hydrogen or C_{1-4}alkyl;
Het^1 represents 2-bora-1,3-dioxolanyl;
Ar^4 represents phenyl; Ar^5 represents phenyl;
Ar^6 represents phenyl optionally substituted with nitro.

6. A compound according to any one of claims 1 to 5 wherein X^2 substituent is at position 2', the R^1 substituent represents hydrogen or halo and is at position 4', the R^2 substituent represents halo and is at position 5', the R^3 substituent is at position 2 and the R^4 substituent at position 7 of the structure of formula (I)

7. A kinase inhibitor of formula (I).

8. A compound as claimed in any one of claims 1 to 6 for use as a medicine.

9. Use of a compound as claimed in any one of claims 1 to 6 in the manufacture of a medicament for treating cell proliferative disorders such as atherosclerosis, restenosis and cancer.

10. 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.

11. A compound according to claim 1 wherein;

Y represents -C_{1-2}alkyl-NR^{23}-CO-$CR^{16}R^{17}$-NH

12. A compound according to claim 1 wherein;

R^{13} represents C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl

13. A compound according to claim 1 wherein;

Het^1 represents 2-bora-1,3-dioxolanyl optionally substituted with one or where possible two, three, four or more substituents selected from 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-.

14. A compound according to claim 1 wherein;

R^4 represents C_{1-4}alkyloxy substituted with at least one substituent selected from C_{1-4}alkyloxy-C_{1-4}alkyloxy-, $NR^{37}R^{38}$-carbonyloxy-, Het^5-carbonyloxy-, NR^7R^8, NR^9R^{10}-carbonyl-, Het^3-carbonyl-, Het^{13}-oxy- or Het^2-; wherein

R^8 represents Het^7-aminocarbonyl-; Het^9-oxycarbonyl-; Het^{10}-sulfonyl-; C_{1-4}alkyloxycarbonyl; mono- or di(C_{1-4}alkyl)aminocarbonyl-; mono- or di(C_{1-4}alkyl)aminocarbonyl substituted with C_{1-4}alkylsulfonyl-; or

C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from C_{1-4}alkylsulfonyl, hydroxy- and C_{1-4}alkyloxy-; or

R^8 represents C_{1-4}alkyl substituted with one or more substituents selected from hydroxy C_{1-4}alkylsulfonyl-, $NR^{25}R^{26}$, aminocarbonyloxy-, C_{1-4}alkylcarbonyloxy-, aminocarbonyl-, C_{1-4}alkyloxy-C_{1-4}alkyloxy-, and Het^{11};

Het^{13} represents C_{1-6}alkyloxycarbonyl optionally substituted with phenyl or R^{13} represents Ar^6-sulfonyl or Het^{24}-C_{1-4}alkylcarbonyl; in particular morpholinyl-C_{1-4}alkyl; and

Het^2 represents a heterocycle selected from morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl or thiomorpholinyl said Het^2 substituted with one or where possible two or more substituents selected from C_{1-4}alkyl- substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-; or

C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-; or

C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or

C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or

Het^2 represents 1,1-dioxothiomorpholinyl optionally substituted with C_{1-4}alkyl- optionally substituted with one or more substituents selected from $NR^{27}R^{28}$, C_{1-4}alkylsulfonyl, aminocarbonyloxy-, aminocarbonyl- and mono- or di(C_{1-4}alkyl)aminocarbonyl-; or

C_{1-4}alkyloxy- optionally substituted with C_{1-4}alkyloxy-; or

C_{1-4}alkyloxycarbonyl optionally substituted with one or more substituents selected from hydroxy, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-; or

C_{1-4}alkylcarbonyl optionally substituted with one or more substituents selected from hydroxy-, C_{1-4}alkyloxy- and C_{1-4}alkylsulfonyl-.