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(54) Title: ISOTHIOUREA DERIVATIVES

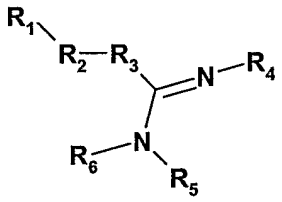
(57) Abstract: The present invention relates to isothiourea derivatives, processes for their production, their uses, in particular in transplantation, autoimmune or infectious diseases, and pharmaceutical compositions containing them.

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Isothiourea derivatives

The present invention relates to isothiourea derivatives, processes for their production, their uses and pharmaceutical compositions containing them.

More particularly, the present invention provides a compound of formula I

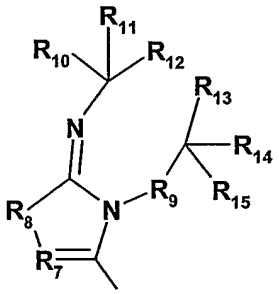


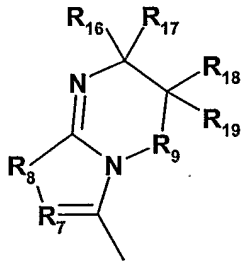
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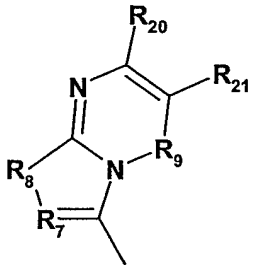
wherein

R_1 is a residue of formula (a), (b) or (c)

(a) (b) (c)







R_2 is $-(CR_{22}R_{23})_{1-3}-$ or -C(O)-;

each of R_3 and R_8 independently is S; O; or NR_{24};

each of R_4 and R_5 independently is optionally R_{25}-substituted C_3-C_{12} cycloalkyl, C_1-C_{12} alkyl or saturated C_{8-12} polycyclic residue; or optionally R_{26}- and/or R_{27}-substituted aryl, arylC_{1-4}alkyl or heteroaryl; wherein up to 4 carbon atoms of R_4 and/or R_5 are optionally substituted by S, O or NR_{24};

R_6 is H; C_1-C_6 alkyl; C_3-C_6 cycloalkyl; or optionally R_{26}- and/or R_{27}-substituted aryl, arylC_{1-4}alkyl or heteroaryl;

R_7 is CR_{28} or N;

R_9 is a direct bond; $-(CR_{22}R_{23})_{1-2}-$; or NR_{24};

each of R_{10-23} and R_{28} independently is H; F; Cl; Br; C_1-C_6 alkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; optionally R_{26}- and/or R_{27}-substituted aryl or heteroaryl; $CONR_{29}R_{30}$; $COOR_{29}$; CN; NO_2; or OR_{31}; or

two of R_{10-19} which are attached to the same carbon atom, together with the carbon atom to which they are attached, form a 3-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; or

R_{17} and R_{18}, together with the C atoms to which they are attached, form a 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; or

R_{20} and R_{21}, together with the carbon atoms to which they are attached, form an optionally R_{26}- and/or R_{27}-substituted aryl or heteroaryl;

each of R_{24}, R_{29} and R_{30} independently is H; C_1-C_6 alkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_7 cycloalkyl; or optionally R_{26}- and/or R_{27}-substituted aryl, arylC_{1-4}alkyl or heteroaryl;

R_{25} represents 1 to 4 substituents each independently having one of the significances given for R_{10-23} above;

R_{26} represents 1 to 4 substituents each independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_3-C_6 cycloalkenyl; C_2-C_6 alkynyl; aryl; heteroaryl; heteroaryl N-oxide ; F; Cl; Br; I; OH; OR_4; $CONH_2$; $CONHR_4$; $CONR_4R_4$;$OC(O)R_4$; $OC(O)OR_4$; $OC(O)NHR_4$; $OC(O)NR_4R_4$; OSO_2R_4; COOH; $COOR_4$; CF_3; CHF_2; CH_2F; CN; NO_2; NH_2; NHR_4; NR_4R_4; $NHC(O)R_4$; $NR_4C(O)R_4$; $NHC(O)NHR_4$; $NHC(O)NH_2$; $NR_4C(O)NHR_4$; $NR_4C(O)NR_4R_4$; $NHC(O)OR_4$; $NR_4C(O)OR_4$; $NHSO_2R_4$; $N(SO_2R_4)_2$; $NR_4SO_2R_4$; SR_4; $S(O)R_4$; SO_2R_4; $Si(CH_3)_3$ and $B(OC(CH_3)_2)_2$;

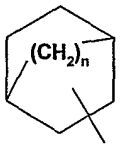
R_{27} represents two adjacent substituents which form an annulated 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S;

R_{31} is C_1-C_6 alkyl; C_3-C_7 cycloalkyl; optionally R_{26}- and/or R_{27}-substituted aryl, arylC_{1-4}alkyl or heteroaryl; or CF_3.

Any alkyl, alkenyl or alkynyl may be linear or branched. Halogeno is F, Cl, Br or I.

By aryl is meant phenyl or naphthyl.

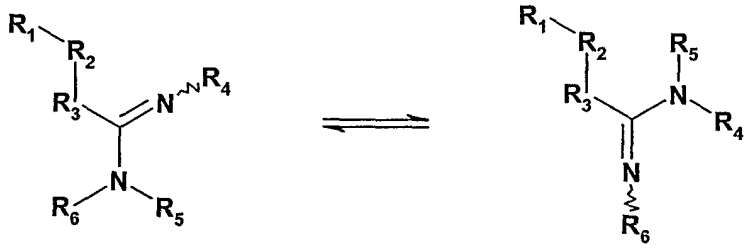
The polycyclic residue may be for example optionally R_{25}-substituted adamantyl, bicyclo[3,2.1]octyl or



wherein n is 1 or 2.

By heteroaryl is meant an aromatic ring system comprising mono-, bi- or tricyclic systems which contains up to 4 heteroatoms independently selected from N, O and S. Examples of heteroaryl include e.g. pyridyl, indolyl, benzothiazolyl, thiazolyl, imidazolyl, benzimidazolyl. Examples of 3 to 7 membered nonaromatic rings containing 1 or 2 heteroatoms include e.g. morpholinyl, piperazinyl, piperidyl.

The compounds of formula I may exist in form of several interconverting tautomers and E/Z isomers, e.g.



They may exist in free form or in salt form, e.g. addition salts with e.g. organic or inorganic acids, for example, hydrochloric acid, acetic acid. When the compounds of formula I have one or more asymmetric centers in the molecule, the present invention is to be understood as embracing the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof.

In the compounds of formula 1, the following significances are preferred individually or in any sub-combination:

1. (a) Each of R_{10-23} and R_{28} independently is H; or C_1-C_6 alkyl;

(b) two of R_{10-19} which are attached to the same carbon atom, together with the carbon atom to which they are attached, form a 3-6 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; or

(c) R_{17} and R_{18}, together with the C atoms to which they attached, form a 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; or

2. R_9 is a direct bond; or $-CR_{22}R_{23}-$;

3. each of R_{24}, R_{29} and R_{30} independently is H; C_1-C_6 alkyl; or C_3-C_7 cycloalkyl;

4. R_7 is CR_{28};

5. R_2 is $-CR_{22}R_{23}-$;

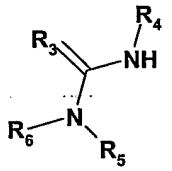
6. each of R_4 and R_5 independently is optionally R_{25}-substituted C_5-C_9 cycloalkyl or C_6-C_{12}alkyl; or adamantyl; wherein optionally up to 4 carbon atoms of R_4 and/or R_5 are substituted by S, O or NR_{24};

7. R_6 is H; or C_1-C_6 alkyl;

8. each of R_3 and R_8 independently is S;

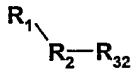
9. arylC_{1-4}alkyl is benzyl;

The invention also covers a process for preparing a compound of formula I comprising reacting a compound of formula II



II

with a compound of formula III



III

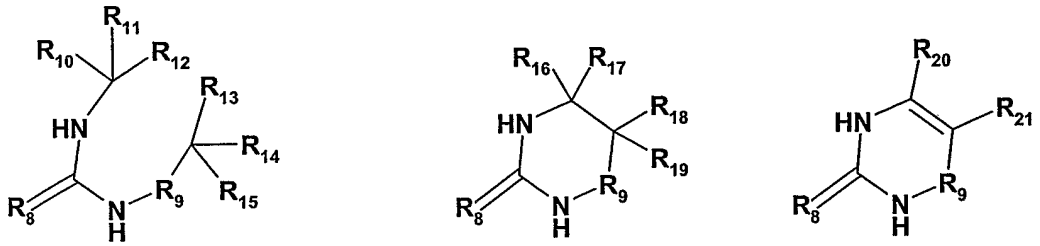
wherein $R_{1\text{-}6}$ are as defined above and R_{32} is a leaving group;

and optionally converting a resultant compound of formula I obtained in free form to a salt form or vice versa.

Preferably R_{32} is halogeno, more preferably chloro.

The compounds of formula III are known or may be prepared by reacting a compound of formula IV (a), (b) or (c)

(a) (b) (c)



wherein R_{8-21} are as defined above,

with 1,3-dichloro-acetone, and recovering the compound of formula III in free or salt form.

The compounds of formulae II and IV are known and can be prepared according to procedures well established in the art.

The following examples illustrate the invention without any limitation.

Example 1

1,3-dicyclohexyl-2-(5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea

A mixture of N,N'-dicyclohexyl thiourea (0.21 g, 1.0 mmol), 3-chloromethyl-5,6-dihydro-imidazo[2,1-b]thiazole (0.72 g, 3.0 mmol) and acetonitrile (10 ml) is refluxed for 4 h. The precipitate is filtered off and crystallized from methanol/ether to give the dihydrochloride of 1,3-dicyclohexyl-2-(5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea. MS/ESI 379 [$M+H^+$]

Example 2

1,3-dicyclohexyl-2-(3-methyl-2-methylimino-2,3-dihydro-thiazol-4-ylmethyl)-isothiourea

1,3-dicyclohexyl-2-(3-methyl-2-methylimino-2,3-dihydro-thiazol-4-ylmethyl)-isothiourea is prepared from 4-chloromethyl-3-methyl-3H-thiazol-2-ylidene-methyl-amine using a procedure analogous to that described in example 1, except that the latter compound is used in place of 3-chloromethyl-5,6-dihydro-imidazo[2,1-b]thiazole. MS/ESI 381 [$M+H^+$].

(4-chloromethyl-3-methyl-3H-thiazol-2-ylidene)-methyl-amine used as starting material is prepared according to the following procedure:

A mixture of N,N'-dimethyl thiourea (1.04 g, 10.0 mmol), 1,3-dichloro acetone (1.27 g, 10.0 mmol) and n-butanol (25 ml) is heated at 140°C for 1 h. The solvent is removed and the residue crystallized from methanol/ether to give the hydrochloride of (4-chloromethyl-3-methyl-3H-thiazol-2-ylidene)-methyl-amine. MS/ESI 177 [M+H$^+$].

Example 3

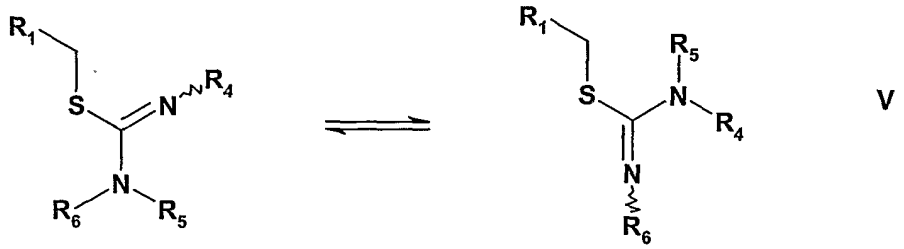
1,3-dicyclohexyl-2-(6,6-dimethyl-5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea

1,3-dicyclohexyl-2-(6,6-dimethyl-5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea is prepared from 3-chloromethyl-6,6-dimethyl-5,6-dihydro-imidazo[2,1-b]thiazole using a procedure analogous to that described in example 1, except that the latter compound is used in place of 3-chloromethyl-5,6-dihydro-imidazo[2,1-b]thiazole. MS/ESI 407 [M+H$^+$].

3-Chloromethyl-6,6-dimethyl-5,6-dihydro-imidazo[2,1-b]thiazole used as starting material is prepared according to the following procedure:

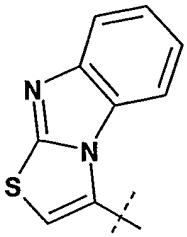
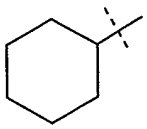
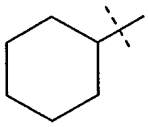
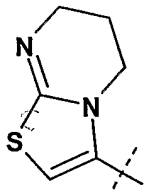
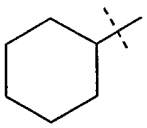
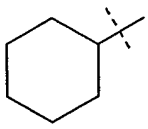
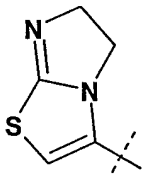
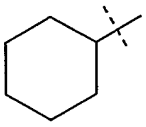
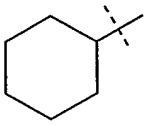
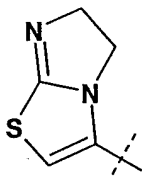
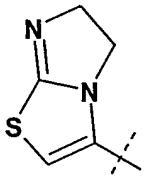
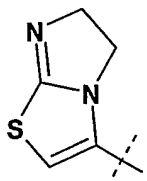
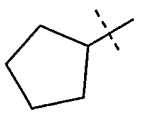
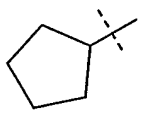
A mixture of 4,4-dimethyl-imidazolidine-2-thione (1.0 g, 7.5 mmol), 1,3-dichloro acetone (1.00 g, 7.5 mmol) and acetonitrile (15 ml) is refluxed for 2 h. The colorless precipitate is filtered off, dried, suspended in 1-methoxy-2-(2-methoxy-ethoxy)-ethane and, subsequently, heated at 140°C for 2 h. The precipitate is filtered of and washed with ether to give the hydrochloride of 3-chloromethyl-6,6-dimethyl-5,6-dihydro-imidazo[2,1-b]thiazole. MS/ESI 203 [M+H$^+$].

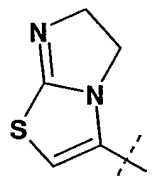
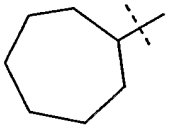
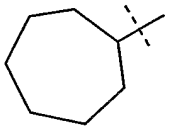
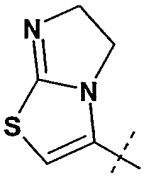
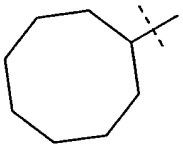
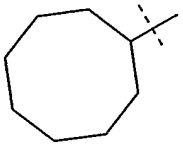
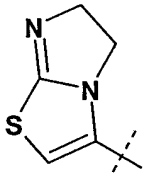
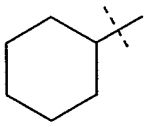
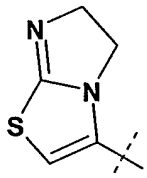
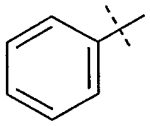
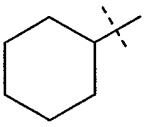
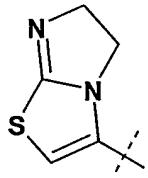
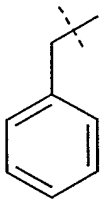
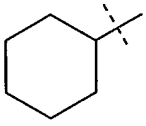
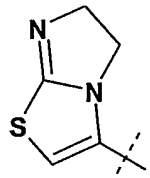
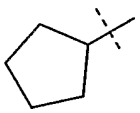
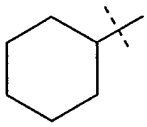
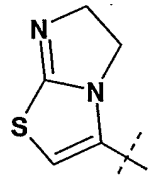
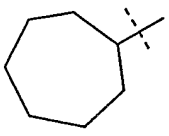
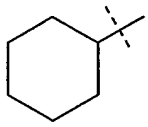
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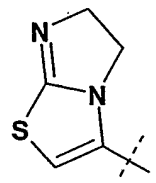
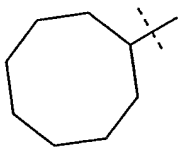
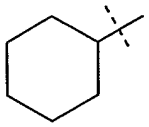
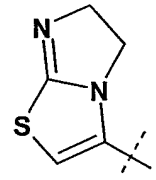
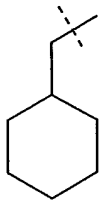
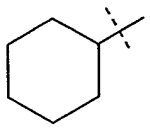
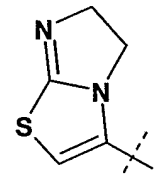
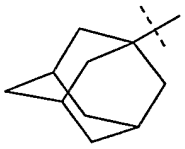
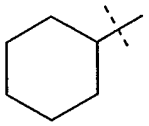
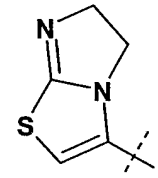
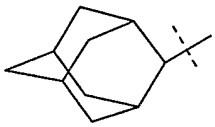
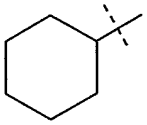
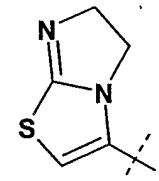
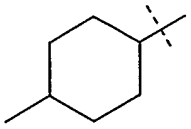
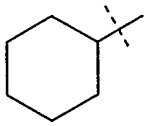
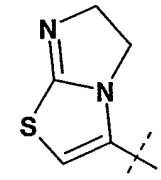
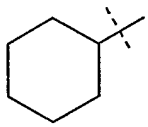
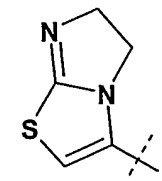
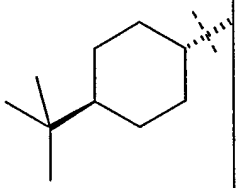
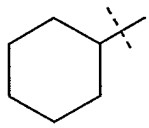


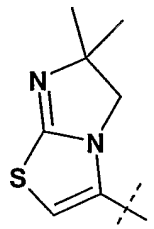
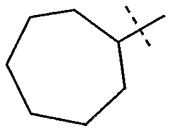
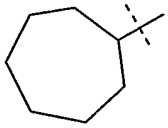
V

are prepared applying similar procedures.

Example	R_1	R_4	R_5	R_6	M^+
4			H		427
5			H		393
6			Me		393
7		Me	H	Me	243
8		isopropyl	H	isopropyl	299
9			H		351

10			H		407
11			H		435
12		H	H		297
13			H		373
14			H		387
15			H		365
16			H		393

17			H		407
18			H		393
19			H		431
20			H		431
21			H		393
22		n-hexyl	H		381
23			H		435

24			H		435

The compounds of formula I in free form or in pharmaceutically acceptable salt form exhibit valuable pharmacological properties, e.g. as CXCR4 antagonists, e.g. as indicated in in vitro tests and therefore indicated for therapy. CXCR4 is a chemokine receptor G protein coupled receptor (GPCR) that is expressed in a variety of normal tissues, including monocytes. SDF-1 (CXCL12) is the cognate ligand of this receptor, and is known to act as a chemoattractant that drives chemotaxis of cells expressing CXCR4.

a) CXCR4 membrane binding assay

Membranes are prepared from the T lymphoblast cell line CEM which endogenously expresses CXCR4. As radioligand 125-I labeled SDF-1α is used. Membranes, radioligand and a compound of formula I are incubated and the amount of bound radioligand determined. The data are reported as IC_{50}, i.e. the concentration of compound required to achieve 50% inhibition of [I-125]SDF-1α binding. In this assay compounds of formula I have an IC_{50} of <50 μM.

b) CXCR4 functional assay – Ca^{2+} mobilization

SDF-1 induced Ca^{2+} mobilization from intracellular stores is measured in CEM cells loaded with the Ca^{2+} - sensing fluorochrome Fluo-4. Fluo-4 loaded cells are incubated with compounds of formula I and then the SDF-1 induced increase in fluorescence is recorded in a fluorescence image plate reader. Inhibitory effects of compounds are expressed as IC_{50} values, representing the concentration of compound which reduces the SDF-1 response by 50%. In this assay compounds of formula I have IC_{50} values of <50 μM.

c) CXCR4 functional assay – chemotaxis

Cell migration (chemotaxis) stimulated by SDF-1 is assessed in Transwell tissue culture inserts with porpous polycarbonate membranes. Target cells (eg.Jurkat T cells, CEM cells or lymphocytes) are added to the upper compartment and the chemokine SDF-1 to the lower

compartment. Compounds of formula I are added to both compartments at the same concentration. Compounds of formula I inhibit SDF-1 induced chemotaxis with IC_{50} values < 50 μM.

The compounds of formula I are, therefore, useful in the prevention and/or treatment of diseases or disorders mediated by interactions between chemokine receptors, e.g. CXCR4, and their ligands, e.g. in transplantation, such as acute or chronic rejection of organ, tissue or cell allo- or xenografts or delayed graft function, autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, vasculitis, pernicious anemia, Sjoegren syndrome, uveitis, psoriasis, alopecia areata and others, allergic diseases, e.g. allergic asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, allergic contact dermatitis, inflammatory diseases optionally with underlying aberrant reactions, e.g. inflammatory bowel disease, Crohn's disease or ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye disease, keratoconjunctivitis, myocarditis or hepatitis, ischemia/reperfusion injury, e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, traumatic shock and others, infectious diseases, e.g. toxic shock (e.g. superantigen induced), septic shock, adult respiratory distress syndrome or viral infections, e.g. binding or entry of the HIV virus into cells expressing CXCR4, or progression of AIDS. By transplantation is meant allo- or xeno grafts of e.g. cells, tissues or solid organs, for example pancreatic islets, stem cells, bone marrow, corneal tissue, neuronal tissue, heart, lung, combined heart-lung, kidney, liver, bowel, pancreas, trachea or oesophagus. Chronic rejection is also named graft vessel disease.

CXCR4 signaling is implicated in the progression, invasion, or metastasis of tumors, e.g. solid tumors. Stromal or epithelial cells associated with primary tumors have been observed to often express SDF-1. CXCR4/SDF-1 interactions are involved in establishment, growth, angiogenesis, or localized invasion of the tumor at the primary site, e.g. blood vessel development, or promotion of entry of tumor cells into the blood or lymphatic circulation via SDF-1 expression by cells associated with blood vessels, e.g. in the early steps of metastasis.

In addition, SDF-1 expression by bone marrow cells promotes recruitment, adherence or proliferation of tumor cells expressing CXCR4 in bone. SDF-1 expression at other sites or tissues plays a similar role in metastasis or establishment of tumors at those sites. Multiple myeloma is an example of a cancer in which recruitment of cells to the bone marrow plays a critical homing, environmental and proliferative role in establishment and progression.

Compounds of the invention are therefore also useful in the prevention or treatment of proliferative diseases, especially malignant proliferative or neoplastic diseases, e.g. tumors, for example brain and other central nervous system tumors (eg. tumors of the meninges, brain, spinal cord, cranial nerves and other parts of central nervous system, e.g. glioblastomas or medulla blastomas); head and/or neck cancer; breast tumors; circulatory system tumors (e.g. heart, mediastinum and pleura, and other intrathoracic organs, vascular tumors and tumor-associated vascular tissue); excretory system tumors (e.g. kidney, renal pelvis, ureter, bladder, other and unspecified urinary organs); gastrointestinal tract tumors (e.g. oesophagus, stomach, small intestine, colon, colorectal, rectosigmoid junction, rectum, anus and anal canal), tumors involving the liver and intrahepatic bile ducts, gall bladder, other and unspecified parts of biliary tract, pancreas, other and digestive organs); head and neck; oral cavity (lip, tongue, gum, floor of mouth, palate, and other parts of mouth, parotid gland, and other parts of the salivary glands, tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx, and other sites in the lip, oral cavity and pharynx); reproductive system tumors (e.g. vulva, vagina, Cervix uteri, Corpus uteri, uterus, ovary, and other sites associated with female genital organs, placenta, penis, prostate, testis, and other sites associated with male genital organs); respiratory tract tumors (e.g. nasal cavity and middle ear, accessory sinuses, larynx, trachea, bronchus and lung, e.g. small cell lung cancer or non-small cell lung cancer); skeletal system tumors (e.g. bone and articular cartilage of limbs, bone articular cartilage and other sites); skin tumors (e.g. malignant melanoma of the skin, non-melanoma skin cancer, basal cell carcinoma of skin, squamous cell carcinoma of skin, mesothelioma, Kaposi's sarcoma); and tumors involving other tissues incluing peripheral nerves and autonomic nervous system, connective and soft tissue, retroperitoneum and peritoneum, eye and adnexa, thyroid, adrenal gland and other endocrine glands and related structures, secondary and unspecified malignant neoplasm of lymph nodes, secondary malignant neoplasm of respiratory and digestive systems and secondary malignant neoplasm of other sites, tumors of blood and lymphatic system (e.g. Hodgkin's disease, Non-Hodgkin's lymphoma, Burkitt's lymphoma, AIDS-related lymphomas, malignant immunoproliferative diseases, multiple myeloma and malignant plasma cell neoplasms, lymphoid leukemia, acute or chronic myeloid leukemia, acute or chronic lymphocytic leukemia,

monocytic leukemia, other leukemias of specified cell type, leukemia of unspecified cell type, other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissues, for example diffuse large cell lymphoma, T-cell lymphoma or cutaneous T-cell lymphoma). Myeloid cancer includes e.g. acute or chronic myeloid leukaemia.

Where hereinbefore and subsequently a tumor, a tumor disease, a carcinoma or a cancer is mentioned, also metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location or locations of the tumor and/or metastasis. The compounds of formula I are particularly indicated for treating tumor invasiveness or symptoms associated with such tumor growth, preventing metastatic spread of tumours or for preventing or inhibiting growth of micrometastasis in a subject in need thereof, especially for treating or preventing metastatic spread of tumors to bone, e.g. to bone marrow. In one embodiment, the compounds of formula I are indicated for preventing or treating metastasis, tumor invasiveness or tumor growth mediated by CXCR4 receptors and/or SDF-1 expression.

In a further embodiment, the compounds of formula I are indicated for inhibiting or controlling deregulated angiogenesis, e.g. angiogenesis mediated by CXCR4 and/or SDF-1, in a subject in need thereof.

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.01 to10 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 1000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from 0.1 to 500 mg, e.g. from ca. 0.5 to 4 mg active ingredient.

The compounds of formula I may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of formula I in free form or in pharmaceutically acceptable salt form in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

The compounds of formula I may be administered in free form or in pharmaceutically acceptable salt form e.g. as indicated above. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

1.1 A method for preventing or treating disorders or diseases mediated by interactions between chemokine receptors, e.g. CXCR4 receptors, and their ligands, e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

1.2 A method for preventing or treating acute or chronic transplant rejection or inflammatory or autoimmune diseases, e.g. as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

1.3 A method for preventing or treating a proliferative disease, e.g. as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

1.4 A method for treating tumor progression, invasiveness or symptoms associated with such tumor growth, preventing metastatic spread of tumours or for preventing or inhibiting growth of micrometastases, or for preventing tumor associated angiogenesis, e.g. as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

1.5 A method for preventing or combating infectious diseases, e.g. viral infection, in particular for preventing or combating the binding or entry of a virus into cells expressing chemokine receptor, e.g. the binding or entry of the HIV virus, such as HIV-1 or HIV-2, into cells expressing CXCR4, or progression of AIDS.

2. A compound of formula I or a pharmaceutically acceptable salt thereof for use as a pharmaceutical, e.g. in any of the methods as indicated under 1.1 to 1.4 above.

3. A pharmaceutical composition, e.g. for use in any of the methods as in 1.1 to 1.4 above comprising a compound of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent or carrier therefor.

4. A compound of formula I or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in any of the method as in to 1.4 above.

The compounds of formula I may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. in immunosuppressive or immunomodulating regimens or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, a chemotherapeutic agent or an anti-infective agent, e.g. an anti-viral agent such as e.g. an anti-retroviral agent or an antibiotic. For example, the compounds of formula I may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; an mTOR inhibitor, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779, ABT578, AP23573, AP23464, AP23675, AP23841 or TAFA-93; an ascomycin having immunosuppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprine; methotrexate; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; a sphingosine-1-phosphate receptor agonist, e.g. FTY720; monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD11a/CD18, CD25, CD27, CD28, CD40. CD45, CD58, CD80, CD86, CD137, ICOS, CD150 (SLAM), OX40, 4-1BB or to their ligands, e.g. CD154, or antagonists thereof; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y ; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or antichemokine antibodies or antichemokine receptor antibodies or low molecular weight chemokine receptor antagonists, e.g. anti MCP-1 antibodies.

The term “anti-viral agent” as used herein includes, but is not limited to, anti-retroviral agent; antibody against virus; e.g. anti-HIV antibody; inhibitor of reverse transcriptase; e.g. inhibitor of HIV reverse transcriptase, especially nucleoside analogues, such as Retrovir® (3’-azido-3’-deoxypyrimidine, Zidovudine) and 3’-azido-3’-deoxythymidine (AZT) from GlaxoSmithKline, HIVID® (2’,3’-dideoxycytidine, Zalcitabine) from Hoffmann-LaRoche, Videx® or VidexEC® (2’,3’dideoxyinosine, Didanosine) from Bristol-Myers-Squibb, Epivir® (Lamivudine) from GlaxoSmithKline, Zerit® (stavudine) from Bristol Myers-Squibb, Viread®

(tenofovir DF) from Gilead, ziagen® (abacavir) from GlaxoSmithKline, Emtriva® (Emtricitabine, FTC) from Gilead Sciences ; or non-nucleoside analogues, such as e.g. rescriptor® (delavirdine) from Pfizer, Sustiva® (Efavirenz) from Bristol Meyer Squibb, viramune® (nevirapine) from Boehringer-Ingelheim;11-cyclopropyl-5,11-dihydro-4-methyl-(6H)-dipyrido[3,2-b;2',3'-e]-[1,4]diazepin-6-one, trisodium phosphonoformate, ammonium-21-tungstenato-9-antimonate, 1-β-D-ribofuranoxyl-1,2,4-triazole-3-carboxamide; inhibitor of viral or retroviral protease, e.g. inhibitor of viral aspartate protease, e.g. inhibitor of HIV protease, such as aganerase® (amprenavir) fromGlaxoSmithKline, reyataz® (atazanavir) from Bristol-Myers Squibb, lexiva® (fosamprenavir) from GSK, Crixivan ® (Indinavir) from Merck & Co.; viracept® (nelfinavir) from Agouron, norvir® (Ritonavir) from Abbott; fortovase® and Invirase® (saquinavir) from Hoffmann-LaRoche; and other compounds such as lasinavir (5(S)-(tert-butoxycarbonylamino)-4(S)-hydroxy-6-phenyl-2(R)(2,3,4-trimethoxyphenylmethyl)-hexanoyl-(L)-valyl-N-(2-metoxy-ethyl)-amide), Adriamycin, KVX-478 from GlaxoWellcome; VX-478 from Vertex; 141W94 from Kissei Pharmaceuticals; AG-1343 from Agouron; KNI-272 from Nippon Mining; U-96988 from Upjohn; BILA-2011BS (Palinavir) from Boehringer-Ingelheim; compounds preventing virus penetration, such as e.g. polymannoacetate; fusion inhibitors, such as e.g. fuzeon® (enfuvirtide, T-20) from Hofffmann-LaRoche; or any combination thereof, such as Epzicom® (Abacavir and Lamivudine) from GlaxoKlineSmith, Trizivir® (Abacavir, Lamivudine and Zidovudine) from GlaxoKlineSmith, Truvada® (Emtricitabine and Tenofir DF) from Gilead Sciences, Combivir® (Lamivudine and Zidovudine) from GlaxoKlineSmith, kaletra® (lopinavir and ritonavir) from Abbott. The term "anti-viral agent" further includes agent which treats the opportunistic infectious which are caused by the immunosuppression resulting from viral infection, e.g. HIV infection.

The term "HIV" as used herein includes, but is not limited to, HIV-1 and HIV-2.

A compound of formula I may also be used to advantage in combination with other antiproliferative agents. Such antiproliferative agents include, but are not limited to aromatase inhibitors, antiestrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, histone deacetylase inhibitors, farnesyl transferase inhibitors, COX-2 inhibitors, MMP inhibitors, mTOR inhibitors, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity and

further anti-angiogenic compounds, gonadorelin agonists, anti-androgens, bengamides, bisphosphonates, antiproliferative antibodies and temozolomide (TEMODAL®).

The term "aromatase inhibitors" as used herein relates to compounds which inhibit the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, vorozole, fadrozole, anastrozole and, very especially, letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark AROMASIN™. Formestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark LENTARON™. Fadrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark AFEMA™. Anastrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark ARIMIDEX™. Letrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark FEMARA™ or FEMAR™. Aminoglutethimide can be administered, e.g., in the form as it is marketed, e.g. under the trademark ORIMETEN™.

A combination of the invention comprising an antineoplastic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive breast tumors.

The term "antiestrogens" as used herein relates to compounds which antagonize the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered, e.g., in the form as it is marketed, e.g. under the trademark NOLVADEX™. Raloxifene hydrochloride can be administered, e.g., in the form as it is marketed, e.g. under the trademark EVISTA™. Fulvestrant can be formulated as disclosed in US 4,659,516 or it can be administered, e.g., in the form as it is marketed, e.g. under the trademark FASLODEX™.

The term "topoisomerase I inhibitors" as used herein includes, but is not limited to topotecan, irinotecan, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/17804). Irinotecan can be administered, e.g., in the form as it is marketed, e.g. under the trademark CAMPTOSAR™. Topotecan can be administered, e.g., in the form as it is marketed, e.g. under the trademark HYCAMTIN™.

The term "topoisomerase II inhibitors" as used herein includes, but is not limited to the antracyclines doxorubicin (including liposomal formulation, e.g. CAELYX™), epirubicin,

idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide can be administered, e.g., in the form as it is marketed, e.g. under the trademark ETOPOPHOS™. Teniposide can be administered, e.g., in the form as it is marketed, e.g. under the trademark VM 26-BRISTOL ™. Doxorubicin can be administered, e.g., in the form as it is marketed, e.g. under the trademark ADRIBLASTIN™. Epirubicin can be administered, e.g., in the form as it is marketed, e.g. under the trademark FARMORUBICIN™. Idarubicin can be administered, e.g., in the form as it is marketed, e.g. under the trademark ZAVEDOS™. Mitoxantrone can be administered, e.g., in the form as it is marketed, e.g. under the trademark NOVANTRON™.

The term "microtubule active agents" relates to microtubule stabilizing and microtubule destabilizing agents including, but not limited to the taxanes paclitaxel and docetaxel, the vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolide and epothilones, such as epothilone B and D. Docetaxel can be administered, e.g., in the form as it is marketed, e.g. under the trademark TAXOTERE™. Vinblastine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark VINBLASTIN R.P.™. Vincristine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark FARMISTIN™. Discodermolide can be obtained, e.g., as disclosed in US 5,010,099.

The term "alkylating agents" as used herein includes, but is not limited to cyclophosphamide, ifosfamide and melphalan. Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark CYCLOSTIN™. Ifosfamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark HOLOXAN™.

The term "histone deacetylase inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity.

The term "farnesyl transferase inhibitors" relates to compounds which inhibit the farnesyl transferase and which possess antiproliferative activity.

The term "COX-2 inhibitors" relates to compounds which inhibit the cyclooxygenase type 2 enyzme (COX-2) and which possess antiproliferative activity such as celecoxib (Celebrex®), rofecoxib (Vioxx®) and lumiracoxib (COX189).

The term "MMP inhibitors" relates to compounds which inhibit the matrix metalloproteinase (MMP) and which possess antiproliferative activity.

The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

The term "antineoplastic antimetabolites" includes, but is not limited to 5-fluorouracil, tegafur, capecitabine, cladribine, cytarabine, fludarabine phosphate, fluorouridine, gemcitabine, 6-mercaptopurine, hydroxyurea, methotrexate, edatrexate and salts of such compounds, and furthermore ZD 1694 (RALTITREXED™), LY231514 (ALIMTA™), LY264618 (LOMOTREXOL™) and OGT719.

The term "platin compounds" as used herein includes, but is not limited to carboplatin, cis-platin and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark CARBOPLAT™. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark ELOXATIN™.

The term "compounds decreasing the protein kinase activity and further anti-angiogenic compounds" as used herein includes, but is not limited to compounds which decrease the activity of e.g. the Vascular Endothelial Growth Factor (VEGF), the Epidermal Growth Factor (EGF), c-Src, protein kinase C, Platelet-derived Growth Factor (PDGF), Bcr-Abl tyrosine kinase, c-kit, Flt-3 and Insulin-like Growth Factor I Receptor (IGF-IR) and Cyclin-dependent kinases (CDKs), and anti-angiogenic compounds having another mechanism of action than decreasing the protein kinase activity.

Compounds which decrease the activity of VEGF are especially compounds which inhibit the VEGF receptor, especially the tyrosine kinase activity of the VEGF receptor, and compounds binding to VEGF, and are in particular those compounds, proteins and monoclonal antibodies generically and specifically disclosed in WO 98/35958 (describing compounds of formula I), WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819, WO 01/55114, WO 01/58899 and EP 0 769 947; those as described by M. Prewett et al in Cancer Research 59 (1999) 5209-5218, by F. Yuan et al in Proc. Natl. Acad. Sci. USA, vol. 93, pp. 14765-14770, December 1996, by Z. Zhu et al in Cancer Res. 58, 1998, 3209-3214, and by J. Mordenti et al in Toxicologic Pathology, vol. 27, no. 1, pp 14-21, 1999; in WO 00/37502 and WO 94/10202; Angiostatin™, described by M. S. O'Reilly et al, Cell 79, 1994, 315-328; and Endostatin™, described by M. S. O'Reilly et al, Cell 88, 1997, 277-285;

compounds which decrease the activity of EGF are especially compounds which inhibit the EGF receptor, especially the tyrosine kinase activity of the EGF receptor, and compounds

binding to EGF, and are in particular those compounds generically and specifically disclosed in WO 97/02266 (describing compounds of formula IV), EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/33980;

compounds which decrease the activity of c-Src include, but are not limited to, compounds inhibiting the c-Src protein tyrosine kinase activity as defined below and to SH2 interaction inhibitors such as those disclosed in WO97/07131 and WO97/08193;

compounds inhibiting the c-Src protein tyrosine kinase activity include, but are not limited to, compounds belonging to the structure classes of pyrrolopyrimidines, especially pyrrolo[2,3-d]pyrimidines, purines, pyrazopyrimidines, especially pyrazo[3,4-d]pyrimidines, pyrazopyrimidines, especially pyrazo[3,4-d]pyrimidines and pyridopyrimidines, especially pyrido[2,3-d]pyrimidines. Preferably, the term relates to those compounds disclosed in WO 96/10028, WO 97/28161, WO97/32879 and WO97/49706;

compounds which decreases the activity of the protein kinase C are especially those staurosporine derivatives disclosed in EP 0 296 110 (pharmaceutical preparation described in WO 00/48571) which compounds are protein kinase C inhibitors;

further specific compounds that decrease protein kinase activity and which may also be used in combination with the compounds of the present invention are Imatinib (Gleevec®/Glivec®), midostaurin, Iressa™ (ZD1839), PKI166, Vatalanib, ZD6474, GW2016, CHIR-200131, CEP-7055/CEP-5214, CP-547632 and KRN-633;

anti-angiogenic compounds having another mechanism of action than decreasing the protein kinase activity include, but are not limited to e.g. thalidomide (THALOMID), celecoxib (Celebrex), SU5416 and ZD6126.

The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin is disclosed in US 4,100,274 and can be administered, e.g., in the form as it is marketed, e.g. under the trademark ZOLADEX™.

Abarelix can be formulated, e.g. as disclosed in US 5,843,901.

The term "anti-androgens" as used herein includes, but is not limited to bicalutamide (CASODEX™), which can be formulated, e.g. as disclosed in US 4,636,505.

The term "bengamides" relates to bengamides and derivatives thereof having aniproliferative properties.

The term "bisphosphonates" as used herein includes, but is not limited to etridonic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, ibandronic acid, risedronic acid and zoledronic acid. "Etridonic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark DIDRONEL™. "Clodronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONEFOS™. "Tiludronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark SKELID™. "Pamidronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark AREDIA™. "Alendronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark FOSAMAX™. "Ibandronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONDRANAT™. "Risedronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark ACTONEL™. "Zoledronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark ZOMETA™.

The term "antiproliferative antibodies" as used herein includes, but is not limited to trastuzumab (Herceptin™), Trastuzumab-DM1, erlotinib (Tarceva™), bevacizumab (Avastin ™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 Antibody.

For the treatment of acute myeloid leukemia (AML), compounds of formula I can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of formula I can be administered in combination with e.g. farnesyltransferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and midostaurin.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

The above-mentioned compounds, which can be used in combination with a compound of formula I, can be prepared and administered as described in the art such as in the documents cited above.

Where the compounds of formula I are administered in conjunction with other immunosuppressive / immunomodulatory, anti-inflammatory, antiproliferative, anti-infective, anti-viral or chemotherapeutic therapy, dosages of the co-administered immunosuppressant, immunomodulatory, anti-inflammatory, antiproliferative, anti-infective, anti-viral or

chemotherapeutic compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth. In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a compound of formula I and at least a second drug substance, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory, antiproliferative, antineoplatic anti-infective, anti-viral, antibiotic or chemotherapeutic drug, e.g. as indicated above.

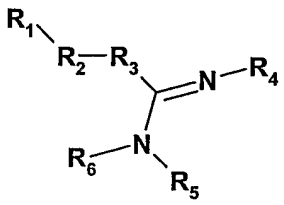
6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a CXCR4 antagonist, e.g. a compound of formula I as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory, antiproliferative, anti-infective or chemotherapeutic drug. The kit may comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, e.g. viral agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, e.g. viral agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Claims

1. A compound of formula I

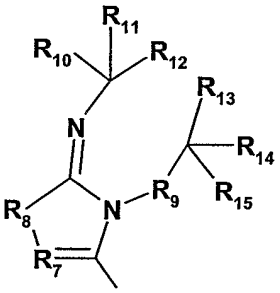


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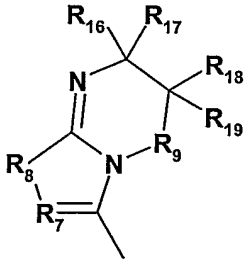
wherein

R_1 is a residue of formula (a), (b) or (c)

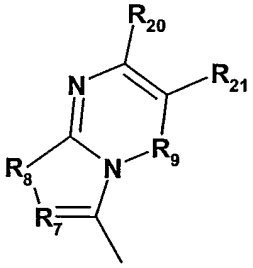
(a)



(b)



(c)



R_2 is $-(CR_{22}R_{23})_{1-3}-$ or -C(O)-;

each of R_3 and R_8 independently is S; O; or NR_{24};

each of R_4 and R_5 independently is optionally R_{25}-substituted C_3-C_{12} cycloalkyl, C_1-C_{12} alkyl or saturated C_{8-12} polycyclic residue; or optionally R_{26}- and/or R_{27}-substituted aryl, arylC_{1-4}alkyl or heteroaryl; wherein up to 4 carbon atoms of R_4 and/or R_5 are optionally substituted by S, O or NR_{24};

R_6 is H; C_1-C_6 alkyl; C_3-C_6 cycloalkyl; or optionally R_{26}- and/or R_{27}-substituted aryl, arylC_{1-4}alkyl or heteroaryl;

R_7 is CR_{28} or N;

R_9 is a direct bond; $-(CR_{22}R_{23})_{1-2}-$; or NR_{24};

each of R_{10-23} and R_{28} independently is H; F; Cl; Br; C_1-C_6 alkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; optionally R_{26}- and/or R_{27}-substituted aryl or heteroaryl; $CONR_{29}R_{30}$; $COOR_{29}$; CN; NO_2; or OR_{31}; or

two of R_{10-19} which are attached to the same carbon atom, together with the carbon atom to which they are attached, form a 3-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; or

R_{17} and R_{18}, together with the C atoms to which they are attached, form a 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; or

R_{20} and R_{21}, together with the carbon atoms to which they are attached, form an optionally R_{26}- and/or R_{27}-substituted aryl or heteroaryl;

each of R_{24}, R_{29} and R_{30} independently is H; C_1-C_6 alkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_7 cycloalkyl; or optionally R_{26}- and/or R_{27}-substituted aryl, arylC_{1-4}alkyl or heteroaryl;

R_{25} represents 1 to 4 substituents each independently having one of the significances given for R_{10-23} above;

R_{26} represents 1 to 4 substituents each independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_3-C_6 cycloalkenyl; C_2-C_6 alkynyl; aryl; heteroaryl; heteroaryl N-oxide ; F; Cl; Br; I; OH; OR_4; $CONH_2$; $CONHR_4$; $CONR_4R_4$;$OC(O)R_4$; $OC(O)OR_4$; $OC(O)NHR_4$; $OC(O)NR_4R_4$; OSO_2R_4; COOH; $COOR_4$; CF_3; CHF_2; CH_2F; CN; NO_2; NH_2; NHR_4; NR_4R_4; $NHC(O)R_4$; $NR_4C(O)R_4$; $NHC(O)NHR_4$; $NHC(O)NH_2$; $NR_4C(O)NHR_4$; $NR_4C(O)NR_4R_4$; $NHC(O)OR_4$; $NR_4C(O)OR_4$; $NHSO_2R_4$; $N(SO_2R_4)_2$; $NR_4SO_2R_4$; SR_4; $S(O)R_4$; SO_2R_4; $Si(CH_3)_3$ and $B(OC(CH_3)_2)_2$;

R_{27} represents two adjacent substituents which form an annulated 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S;

R_{31} is C_1-C_6 alkyl; C_3-C_7 cycloalkyl; optionally R_{26}- and/or R_{27}-substituted aryl, arylC_{1-4}alkyl or heteroaryl; or CF_3;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is selected from 1,3-Dicyclohexyl-2-(5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea, 1-Cyclohexyl-3-cyclopentyl-2-(5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea,1-Cycloheptyl-3-cyclohexyl-2-(5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea,1,3-Dicycloheptyl-2-(5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea, 1-Cyclohexyl-3-cyclooctyl-2-(5,6-dihydro-

imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea,1,3-Dicyclohexyl-2-(6,6-dimethyl-5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea,1,3-Dicyclooctyl-2-(5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea and 1,3-Dicycloheptyl-2-(6,6-dimethyl-5,6-dihydro-imidazo[2,1-b]thiazol-3-ylmethyl)-isothiourea.

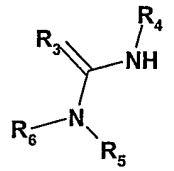
3. A pharmaceutical composition comprising a compound according to claim 1 in free form or in a pharmaceutically acceptable salt form in association with a pharmaceutically acceptable diluent or carrier therefor.

4. Use of a compound according to claimed in claim 1 in free form or in a pharmaceutically acceptable salt form, for the manufacture of a medicament to prevent or treat disorders or diseases mediated by interactions between chemokine receptors, acute or chronic transplant rejection, inflammatory diseases, autoimmune diseases or proliferative diseases.

5. Use of a compound according to claimed in claim 1 in free form or in a pharmaceutically acceptable salt form, for the manufacture of a medicament to prevent or inhibit tumor invasiveness, symptoms associated with tumor growth, metastatic spread of tumours, tumor-associated angiogenesis or growth of micrometastases.

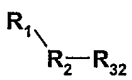
6. Use of a compound as claimed in claim 1 or in claim 2, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament in preventing or combating an infectious diseases, in particular viral infections or progression of AIDS.

7. A process for preparing a compound of formula I comprising reacting a compound of formula II



II

with a compound of formula III



III

wherein R_1 to R_6 are as defined in claim 1 and R_{32} is a leaving group;

and optionally converting a resultant compound of formula I obtained in free form to a salt form or vice versa.

8. A pharmaceutical combination comprising a compound according to claim 1 or claim 2 in free form or in a pharmaceutically acceptable salt form and a further agent selected from immunosuppressive, immunomodulating, anti-inflammatory, antiproliferative, antineoplatic, chemotherapeutic, anti-infective, anti-viral, and antibiotic agents, and agents for the treatment of acute myeloid leukemia.

9. Combination according to claim 8 comprising an antiretroviral agent, in particular an anti-HIV agent.

10. Use of a combination according to claim 9 for the manufacture of a medicament for preventing or combating an infectious disease, in particular viral infection or progression of AIDS.

11. A method of treatment or prevention of any of the following conditions:

i) disorders or diseases mediated by interactions between chemokine receptors,

ii) acute or chronic transplant rejections,

iii) inflammatory or autoimmune diseases,

iv) proliferative diseases,

v) symptoms associated with tumor invasiveness or tumor growth,

vi) metastatic spreads of tumours, tumor-associated angiogenesis and growths of micrometastases,

vii) infectious diseases, in particular viral infections, in particular binding or entry of HIV virus, or progression of AIDS,

comprising administering to said subject a therapeutically effective amount of a compound according to claim 1 or claim 2, or a or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 3.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/42 C07D513/04 A61K31/429 A61K31/425 A61P29/00
A61P35/00 A61P37/00
//(C07D513/04,277:00,235:00),(C07D513/04,277:00,239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 881 015 A (BLACK ET AL) 29 April 1975 (1975-04-29) claims 1,8,11	1,3,4,11
A	US 4 098 898 A (DURANT ET AL) 4 July 1978 (1978-07-04) column 4, line 19 - line 33; claims 1,18,19; examples	1,3,4,11
A	US 4 293 549 A (RACHLIN ET AL) 6 October 1981 (1981-10-06) column 2, line 14 - line 16; claims 1,16; tables	1,3,4,11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2005	08/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hass, C

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/46187 A (ORIDIGM CORPORATION; VERMEULIN, NICOLAAS, M., J; BURNS, MARK, R; WEBB,) 10 August 2000 (2000-08-10) page 32, no. 1284; page 33, no. 1354; page 35, no. 1318, 1317; claims 1,25,27; figures 1,4 abstract	1,3,4,11
A	US 4 041 167 A (MOSER ET AL) 9 August 1977 (1977-08-09) claims 1,7; tables	1,3,4,11
A	US 4 556 669 A (NISHIO ET AL) 3 December 1985 (1985-12-03) claims; examples; tables	1,3,4,11
A	US 4 736 038 A (YAMAMOTO ET AL) 5 April 1988 (1988-04-05) abstract; examples	1,3,4,11
A	US 3 542 802 A (ROBERT C. TWEIT) 24 November 1970 (1970-11-24) abstract; examples	1,3,4,11
A	GB 2 031 426 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES LTD) 23 April 1980 (1980-04-23) page 3, line 55 - page 5, line 12; claims 1,13	1,3,4,11
A	DATABASE WPI Section Ch, Week 200240 Derwent Publications Ltd., London, GB; Class B02, AN 2002-372036 XP002338086 -& WO 02/24711 A1 (NIKKEN CHEM CO LTD) 28 March 2002 (2002-03-28) page 11; examples 1-4,8-11,18-25	1,3,4,11
A	WO 02/072585 A (GRUENENTHAL GMBH; GERLACH, MATTHIAS; MAUL, CORINNA; JAGUSCH, UTZ-PETER) 19 September 2002 (2002-09-19) page 56, examples 133-135, 139; claims 1,14,15	1,3
A	MELLOR J M ET AL: "A General Route to Cyclic Amidines and Isothioureas Based on Formal Aza Diels Alder Reactions of Aminoheterocycles" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 37, no. 15, 8 April 1996 (1996-04-08), pages 2619-2622, XP004029751 ISSN: 0040-4039 page 2619	1,4

INTERNATIONAL SEARCH REPORT

International application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/002014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3881015 A	29-04-1975	BE 758146 A1	28-04-1971
		CA 954522 A1	10-09-1974
		CA 945171 A2	09-04-1974
		CA 983853 A2	17-02-1976
		CH 544087 A	28-12-1973
		CH 529751 A	31-10-1972
		DE 2053175 A1	08-07-1971
		FR 2070178 A5	10-09-1971
		GB 1305546 A	07-02-1973
		NL 7015660 A	04-05-1971
		SE 390967 B	31-01-1977
		US 3868457 A	25-02-1975
		US 3736331 A	29-05-1973
		US 3881016 A	29-04-1975
		US 3968216 A	06-07-1976
		US 4048319 A	13-09-1977
		US 4088769 A	09-05-1978
		DK 140938 B	10-12-1979
		ES 385015 A1	16-03-1973
		ES 387088 A1	16-06-1973
		FI 56001 B	31-07-1979
		IE 35577 B1	31-03-1976
		IE 35578 B1	31-03-1976
		IE 34882 B1	17-09-1975
		IL 35518 A	31-07-1978
		IL 46216 A	31-07-1978
		IN 142986 A1	17-09-1977
		JP 49046307 B	09-12-1974
		NO 133197 B	15-12-1975
		NO 134463 B	05-07-1976
		PH 10563 A	28-06-1977
		SE 376613 B	02-06-1975
		SU 419026 A3	05-03-1974
		SU 382280 A3	22-05-1973
		SU 393828 A3	10-08-1973
		ZA 7007151 A	28-07-1971
US 4098898 A	04-07-1978	GB 1553070 A	19-09-1979
		AT 356131 B	10-04-1980
		AT 361576 A	15-09-1979
		AT 507879 A	15-03-1983
		AU 503525 B2	06-09-1979
		AU 1419576 A	24-11-1977
		BE 841814 A1	16-11-1976
		CA 1076581 A1	29-04-1980
		CH 624941 A5	31-08-1981
		CH 626883 A5	15-12-1981
		DE 2621834 A1	02-12-1976
		DK 206576 A ,B,	22-11-1976
		DK 515379 A	04-12-1979
		FR 2311536 A1	17-12-1976
		IE 44062 B1	12-08-1981
		IL 49528 A	30-11-1980
		JP 51141865 A	07-12-1976
		NL 7605405 A	23-11-1976
		SE 419544 B	10-08-1981
		SE 7605620 A	22-11-1976
		US 4247558 A	27-01-1981

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/002014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4098898 A		US 4276301 A	30-06-1981
		US 4347250 A	31-08-1982
		US 4333946 A	08-06-1982
		US 4440775 A	03-04-1984
		US 4166856 A	04-09-1979
		US 4192879 A	11-03-1980
		ZA 7602536 A	27-04-1977
		LU 74979 A1	19-01-1977
US 4293549 A	06-10-1981	AT 366368 B	13-04-1982
		AT 773278 A	15-08-1981
		AU 517670 B2	20-08-1981
		AU 4137678 A	17-05-1979
		BE 871807 A1	07-05-1979
		CA 1120929 A1	30-03-1982
		CH 645354 A5	28-09-1984
		DE 2847792 A1	10-05-1979
		DK 493378 A ,B,	08-05-1979
		ES 474900 A1	16-04-1980
		FI 783327 A ,B,	08-05-1979
		FR 2407930 A1	01-06-1979
		GB 2009155 A ,B	13-06-1979
		GR 65010 A1	12-06-1980
		IE 47458 B1	21-03-1984
		IT 1100075 B	28-09-1985
		JP 54073784 A	13-06-1979
		JP 63048873 B	30-09-1988
		LU 80476 A1	15-06-1979
		NL 7811035 A	09-05-1979
		NZ 188770 A	31-07-1984
		PH 16296 A	05-09-1983
		PT 68750 A	01-12-1978
		SE 446267 B	25-08-1986
		SE 7811457 A	08-05-1979
		SU 828967 A3	07-05-1981
		YU 257578 A1	21-01-1983
		ZA 7806175 A	31-10-1979
WO 0046187 A	10-08-2000	AU 778343 B2	02-12-2004
		AU 3482900 A	25-08-2000
		CA 2362259 A1	10-08-2000
		EP 1159261 A2	05-12-2001
		JP 2002536357 T	29-10-2002
		WO 0046187 A2	10-08-2000
US 4041167 A	09-08-1977	AU 516452 B2	04-06-1981
		AU 2136277 A	27-07-1978
		BE 850472 A1	18-07-1977
		CA 1095524 A1	10-02-1981
		CA 1127084 A2	06-07-1982
		CH 625249 A5	15-09-1981
		CH 634075 A5	14-01-1983
		DE 2701853 A1	21-07-1977
		FR 2338281 A1	12-08-1977
		GB 1556877 A	28-11-1979
		GB 1556878 A	28-11-1979
		IL 59625 A	31-01-1984
		IL 59626 A	31-01-1984

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/002014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4041167 A		JP 52106893 A	07-09-1977
		NL 7700531 A	21-07-1977
		US 4224334 A	23-09-1980
		US 4103016 A	25-07-1978
		US 4110451 A	29-08-1978
		ZA 7700265 A	22-02-1978
US 4556669 A	03-12-1985	JP 57169490 A	19-10-1982
		CA 1175842 A1	09-10-1984
		CH 648319 A5	15-03-1985
		DE 3213027 A1	27-01-1983
		ES 8307826 A1	01-11-1983
		FR 2503713 A1	15-10-1982
		GB 2099419 A ,B	08-12-1982
		IT 1190764 B	24-02-1988
		NL 8201525 A	01-11-1982
		US 4629793 A	16-12-1986
US 4736038 A	05-04-1988	JP 1686374 C	11-08-1992
		JP 3053316 B	14-08-1991
		JP 61251686 A	08-11-1986
		JP 1719995 C	14-12-1992
		JP 4007749 B	12-02-1992
		JP 61251687 A	08-11-1986
		JP 1719996 C	14-12-1992
		JP 4007750 B	12-02-1992
		JP 61251688 A	08-11-1986
		CA 1271480 A1	10-07-1990
		DE 3680815 D1	19-09-1991
		EP 0200134 A2	05-11-1986
		US 4910315 A	20-03-1990
US 3542802 A	24-11-1970	NONE	
GB 2031426 A	23-04-1980	JP 55045666 A	31-03-1980
		JP 55049386 A	09-04-1980
		BE 879077 A1	16-01-1980
		CA 1131226 A1	07-09-1982
		CH 644384 A5	31-07-1984
		DE 2939224 A1	17-04-1980
		FR 2437410 A1	25-04-1980
		IT 1167053 B	06-05-1987
		SE 7908024 A	29-03-1980
		US 4244952 A	13-01-1981
WO 0224711 A1	28-03-2002	AU 9024301 A	02-04-2002
		JP 2002167389 A	11-06-2002
WO 02072585 A	19-09-2002	DE 10112197 A1	19-09-2002
		DE 10153344 A1	15-05-2003
		BR 0208244 A	02-03-2004
		CA 2440760 A1	19-09-2002
		CN 1507447 A	23-06-2004
		CZ 20032474 A3	17-12-2003
		WO 02072585 A2	19-09-2002
		EP 1368355 A2	10-12-2003
		HU 0401211 A2	28-10-2004
		JP 2004527508 T	09-09-2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/002014

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 02072585 A		MX	PA03008291 A	11-12-2003
		NO	20034031 A	21-10-2003
		PL	364388 A1	13-12-2004
		SK	11542003 A3	07-07-2004
		US	2004127508 A1	01-07-2004
		ZA	200307963 A	26-07-2004