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(54) **CANCER TREATMENT**

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,100,274	A	7/1978	Dutta et al.	
4,636,505	A	1/1987	Tucker	
4,885,171	A *	12/1989	Surendra et al.	424/122
5,010,099	A	4/1991	Gunasekera et al.	
5,066,493	A	11/1991	Sehgal et al.	424/122
5,093,330	A	3/1992	Caravatti et al.	
5,194,447	A *	3/1993	Kao	514/542
5,206,018	A	4/1993	Sehgal et al.	424/122
5,362,718	A	11/1994	Skotnicki et al.	514/63
5,521,184	A	5/1996	Zimmermann	
5,747,498	A	5/1998	Schnur et al.	
5,792,783	A	8/1998	Tang et al.	
5,843,901	A	12/1998	Roeske	
5,922,730	A	7/1999	Hue et al.	514/291
5,985,890	A *	11/1999	Cottens et al.	514/291
6,333,348	B1 *	12/2001	Vogel et al.	514/449
6,569,463	B2	5/2003	Patel et al.	424/497
6,617,333	B2	9/2003	Rabindran et al.	514/291
6,641,811	B1 *	11/2003	Suthanthiran et al.	424/146.1
6,878,720	B2	4/2005	Altmann et al.	
2002/0098278	A1	7/2002	Bates et al.	427/2.1
2003/0100886	A1	5/2003	Segal et al.	604/509
2003/0100887	A1	5/2003	Scott et al.	604/509

FOREIGN PATENT DOCUMENTS

EP	520722		12/1992
EP	566226		10/1993
EP	787722		8/1997
EP	837063		4/1998
EP	1074263		2/2001
EP	1074263		11/2006
WO	94/09010		4/1994
WO	9410202	A1	5/1994
WO	9503283	A1	2/1995
WO	94/16691		6/1995
WO	95/28406		10/1995
WO	9630347	A1	10/1996
WO	9633980	A1	10/1996
WO	9641807		12/1996
WO	9702266	A1	1/1997
WO	9730034	A1	8/1997
WO	9735575	A1	10/1997
WO	9738983	A1	10/1997
WO	9747317		12/1997
WO	9749688	A1	12/1997
WO	98/09970		3/1998
WO	9810767	A2	3/1998
WO	9811223	A1	3/1998
WO	9811908		3/1998
WO	9835958	A1	8/1998
WO	9917804	A1	4/1999
WO	99038654	A1	8/1999
WO	0009495		2/2000
WO	0027820		5/2000
WO	0037502		6/2000
WO	0059509		10/2000
WO	01/51049		7/2001
WO	0149338		7/2001
WO	0187372		11/2001
WO	0197809		12/2001

(Continued)

OTHER PUBLICATIONS

Lien et al. Therapeutic anti-VEGF antibodies. Therapeutic Antibodies, Handbook of Experimental Pharmacology181. Y. Chernajovsky et al. (eds). 2008; pp. 131-150.*
Wikipedia (http://en.wikipedia.org/wiki/Angiogenesis.*
Zhu et al. ("Inhibition of tumor growth and metastasis by targeting tumor-associated angiogenesis with antagonists to the receptors of vascular endothelial growth factor", Investigational New Drugs, 17, 1999, 195-212).*
Shi et al. ("Rapamycin enhances apoptosis and increases sensitivy to cisplatin in vitro" Cancer Research, 1995, 55, 1982-1988).*
Fossa et al. ("Survival of patients with advanced urothelial cancer treated with cisplatin-based chemotherapy" Britich Journal of Cancer 1996, 74, 1655-1659).*
renal pelvis (medical dictionary definition Dec. 12, 1998, accessed via http://www.mondofacto.com /facts/dictionary?renal+pelvis on May 19, 2011).*

(Continued)

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(57) **ABSTRACT**

Rapamycin derivatives have interesting effects in the treatment of solid tumors, optionally in combination with a chemotherapeutic agent.

FOREIGN PATENT DOCUMENTS

WO	02/05791	1/2002
WO	0213802	2/2002
WO	0240000	5/2002
WO	02/080975	10/2002
WO	02080975	10/2002
WO	02/098416	12/2002

OTHER PUBLICATIONS

Sokoloff et al. "Current Management of Renal Cell Carcinoma" CA Cancer J. Clin. 1996, 46, 284-302.*

Cho et al. ("Current Status of Targeted Therapy for Advanced Renal Cell Carcinoma", Korean Journal of Urology, 2012, 53, 217-228.*

Arecci et al., "Immunosuppressants FK506 and Rapamycin Function as Reversal Agents of the Multidrug Resistance Phenotype", *Blood*, vol. 80, No. 6, pp. 1528-1536 (1992).

Dayanir et al., "Identification of Tyrosine Residues in Vascular Endothelial Growth", *J Biol Chem*, vol. 276, No. 21, pp. 17686-17692 (2001).

Eng et al., "Activity of Rapamycin (AY-22,989) Against Transplated Tumors", *J Antibiotics*, vol. XXXXVII, No. 10, pp. 1231-1237 (1984).

Law et al., "Farnesyltransferase Inhibitor Induces Rapid Growth Arrest and Blocks p70s6k Activation by Multiple Stimuli", *J Biol Chem*, vol. 275, No. 15, pp. 10796-10801 (2000).

Peng et al., "Novel Pyrrolo-quinoline Derivatives as Potent Inhibitors for PI3-Kinase Related Kinases", *Bioorg Med Chem*, vol. 10, No. 1, pp. 167-174 (2002).

Shi et al., "Rapamycin Enhances Apoptosis and Increases Sensitivity to Cisplatin in Vitro", *Cancer Res*, vol. 55, No. 9, pp. 1982-1988 (1995).

Geoerger et al., "Antitumor Activity of the Rapamycin Analog CCI-779 in Human Primitive Neuroectodermal Tumor/Medulloblastoma Models as Single Agent and in Combination Chemotherapy", Cancer Research 61: 1527-1532 (2001).

Guba et al., "Rapamycin inhibits tumor growth and metastasis by antiangiogenesis", Chirugishes Forum Fver Experimentelle und Klinische Forschung: 37-39 (2001).

Zhong et al., "Modulation of Hypoxia-inductible Factor 1-alpha Expression by the Epidermal Growth Factor/ Phosphatidylinositol 3-Kinase/PTEN/AKT/FRAP Pathway in Human Prostate Cancer Cells: Implications for Tumor Angiogenesis and Therapeutics"; Cancer Research 60: 1541-1545 (2000).

Zhong et al. "Modulation of Hypoxia-Inducible Factor 1-alpha Expression by the Epidermal Growth Factor/ Phosphatidylinositol 3-Kinase/PTEN/AKT/ FRAP Pathway . . . ", Cancer Res. 2000, 60(6): 1541-1545.

Geoerger et al. "Antitumor Activity of the Rapamycin Analog CCI-779 in Human Primitive Neuroectodermal Tumor/Medulloblastoma Models as SingleAgent and in Combination Chemotherapy", Cancer Res 2001, 61(4): 1527-1532.

Guba et al. "Rapamycin Inhibits Tumor Growth and Metastasis by Antiangiogenesis", Chirurgisches Forum Fuer Experimentelle and Klinische Forschung, 2001, 37-39.

Fukazawa et al., "U0126 Reverses Ki-ras-mediated Transformation by Blocking Both Mitogen-activated Protein Kinase and p70 S6 Kinase Pathways"; Cancer Research 2000, 60: 2104-2107.

Hallensleben et al., "Identification of a New Metabolite of Macrolide Immunosuppressant, Like Rapamycin and SDZ RAD, Using High Performance Liquid Chromatography and Electrospray Tandem Mass Spectrometry"; J Am Soc Mass Spectrom 2000, 11: 516-525.

Majewski et al., The immunosuppressive macrolide RAD inhibits growth of human Ebstein-Barr virus-transformed B lymphocytes in vitro and in vivo: A potential approact to prevention and treatment of posttransplant lymphoproliferative disorders; PNAS 2000, 97(8): 4285-4290.

Mordenti et al., "Efficacy and Concentration-Response of Murine Anti-VEGF Monoclonal Antibody in Tumor-Bearing Mice and Extrapolation to Humans"; Toxicologic Pathology 1999, 27(1): 14-21.

O'Reilly et al., "Angiostatin: A Novel Angiogenesis Inhibitor That Mediates the Suppression of Metastases by a Lewis Lung Carcinoma"; Cell 1994, 79: 315-328.

O'Reilly et al., "Endostatin: An Endogeneous Inhibitor of Angiogenesis and Tumor Growth"; Cell 1997, 88: 277-285.

Prewett et al., "Antivascular Endothelial Growth Factor Receptor (Fetal Liver Kinase 1) Monocolnal Antibody Inhibits Tumor Angiogenesis and Growth of Several Mouse and Human Tumors"; Cancer Research 1999, 59: 5209-5218.

Yuan et al. "Time-dependent vascular regression and permeability changes in established human tumor xenografts induced by an anti-vascular endothelial growth factor/vascular permeability factor antibody"; Proc. Natl. Acad. Sci. 1996, 93: 14765-14770.

Zhu et al., "Inhibition of Vascular Endothelial Growth Factor-induced Receptor Activation with Anti-Kinase Insert Domain-containing Receptor Single-Chain Antibodies from a Phage Display Library"; Cancer Research 1998, 58: 3209-3214.

Zhaoyou, Modern Oncology 2000, 1st press. (English summary provided) English summary only considered.

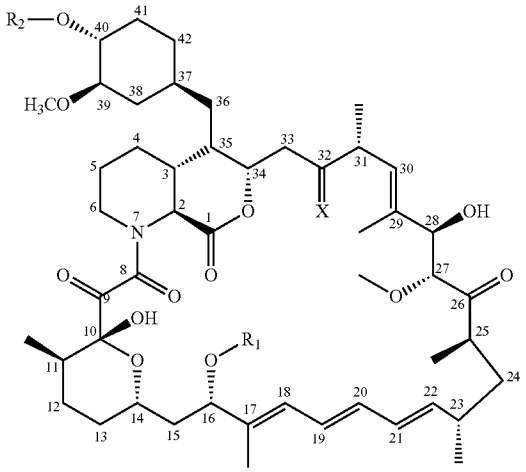
* cited by examiner

CANCER TREATMENT

The present invention relates to a new use, in particular a new use for a compound group comprising rapamycin and derivatives thereof.

Rapamycin is a known macrolide antibiotic produced by *Streptomyces hygroscopicus*. Suitable derivatives of rapamycin include e.g. compounds of formula I

I



wherein
R_1 is CH_3 or C_{3-6}alkynyl,
R_2 is H or —CH_2—CH_2OH, and
X is =O, (H,H) or (H,OH)
provided that R_2 is other than H when X is =O and R_1 is CH_3.

Compounds of formula I are disclosed e.g. in U.S. Pat. Nos. 5,665,772; 6,440,990; 5,985,890; and 6,200,985, which are incorporated herein by reference. They may be prepared as disclosed or by analogy to the procedures described in these references.

Preferred compounds are 32-deoxorapamycin, 16-pent-2-ynyloxy-32-deoxorapamycin, 16-pent-2-ynyloxy-32(S)-dihydro-rapamycin, 16-pent-2-ynyloxy-32(S)-dihydro-40-O-(2-hydroxyethyl)-rapamycin and, more preferably, 40-O-(2-hydroxyethyl)-rapamycin (referred thereafter as Compound A), disclosed as Example 8 in U.S. Pat. Nos. 5,665,772 and 6,440,990.

Compounds of formula I have, on the basis of observed activity, e.g. binding to macrophilin-12 (also known as FK-506 binding protein or FKBP-12), e.g. as described in WO 94/09010, WO 95/16691 or WO 96/41807, been found to be useful e.g. as immunosuppressant, e.g. in the treatment of acute allograft rejection. It has now been found that Compounds of formula I have potent antiproliferative properties which make them useful for cancer chemotherapy, particularly of solid tumors, especially of advanced solid tumors. There is still the need to expand the armamentarium of cancer treatment of solid tumors, especially in cases where treatment with anticancer compounds is not associated with disease regression or stabilization.

In accordance with the particular findings of the present invention, there is provided:

1.1 A method for treating solid tumors in a subject in need

1.2 A method for inhibiting growth of solid tumors in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of formula I.

1.3 A method for inducing tumor regression, e.g. tumor mass reduction, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of formula I.

1.4 A method for treating solid tumor invasiveness or symptoms associated with such tumor growth in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of formula I.

1.5 A method for preventing metastatic spread of tumours or for preventing or inhibiting growth of micrometastasis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a compound of formula I.

By "solid tumors" are meant tumors and/or metastasis (whereever located) other than lymphatic cancer, e.g. 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 binary 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.

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 of the tumor and/or metastasis is.

In a series of further specific or alternative embodiments, the present invention also provides

1.6 A method for the treatment of a disease associated with

effective amount of rapamycin or a derivative thereof, e.g. CCI779, ABT578 or a compound of formula I.

1.7 A method for inhibiting or controlling deregulated angiogenesis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a derivative thereof, e.g. CCI779, ABT578 or a compound of formula I.

1.8 A method for enhancing the activity of a chemotherapeutic agent or for overcoming resistance to a chemotherapeutic agent in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a derivative thereof, e.g. CCI779, ABT578 or a compound of formula I, either concomitantly or sequentially with said chemotherapeutic agent.

1.9 A method according to 1.8 wherein the chemotherapeutic agent is an inhibitor of signal transduction pathways directed either against host cells or processes involved in tumor formation and/or metastases formation or utilised by tumour cells for proliferation, survival, differentiation or development of drug resistance.

1.10 A method as indicated above, wherein rapamycin or a derivative thereof, e.g. CCI779, ABT578 or a compound of formula I is administered intermittently.

CCI779 is a rapamycin derivative, i.e. 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin or a pharmaceutically acceptable salt thereof, and is disclosed e.g. in U.S. Pat. No. 5,362,718. ABT578 is a 40-substituted rapamycin derivative further comprising a diene reduction.

Examples of diseases associated with deregulated angiogenesis include without limitation e.g. neoplastic diseases, e.g. solid tumors. Angiogenesis is regarded as a prerequisite for those tumors which grow beyond a certain diameter, e.g. about 1-2 mm.

In a series of further specific or alternative embodiments, the present invention also provides:

2.1 A compound of formula I for use in any method as defined under 1.1 to 1.5 above.

2.2 Rapamycin or a derivative thereof, e.g. CCI779, ABT578 or a compound of formula I for use in any method as defined under 1.6 to 1.10 above or 7 below.

3.1 A compound of formula I for use in the preparation of a pharmaceutical composition for use in any method as defined under 1.1 to 1.5 above.

3.2 Rapamycin or a derivative thereof, e.g. CCI779, ABT578 or a compound of formula I for use in the preparation of a pharmaceutical composition for use in any method as defined under 1.6 to 1.10 above or 7 below.

4.1 A pharmaceutical composition for use in any method as defined under 1.1 to 1.5 above comprising a compound of formula I together with one or more pharmaceutically acceptable diluents or carriers therefor.

4.2 A pharmaceutical composition for use in any method as defined under 1.6 to 1.10 above or 7 below comprising rapamycin or a derivative thereof, e.g. CCI779, ABT578 or a compound of formula I, e.g. Compound A, together with one or more pharmaceutically acceptable diluents or carriers therefor.

5.1 A pharmaceutical combination comprising a) a first agent which is rapamycin or a derivative thereof, e.g. CCI779, ABT578 or a compound of formula I, e.g. Compound A, and b) a co-agent which is a chemotherapeutic agent, e.g. as defined hereinafter.

5.2 A pharmaceutical combination comprising an amount of a) a first agent which is rapamycin or a derivative thereof, [illegible] peutic agent selected from the compounds defined under paragraph (iv) or (v) below, to produce a synergistic therapeutic effect.

6. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of rapamycin or a derivative thereof, e.g. CCI779, ABT578 or a compound of formula I, e.g. Compound A, and a second drug substance, said second drug substance being a chemotherapeutic agent, e.g. as indicated hereinafter.

7. A method for treating post-transplant lymphoproliferative disorders or a lymphatic cancer, e.g. for treating tumor invasiveness or symptoms associated with such tumor growth in a subject in need thereof, comprising co-administering to said subject, e.g. concomitantly or in sequence, of rapamycin or a derivative thereof, e.g. CCI779, ABT578 or a compound of formula I, e.g. Compound A, and a second drug substance, said second drug substance being a chemotherapeutic agent, e.g. as indicated hereinafter.

By "lymphatic cancer" are meant e.g. 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, 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, haematopoletic and related tissues, for example diffuse large cell lymphoma, T-cell lymphoma or cutaneous T-cell lymphoma).

By the term "chemotherapeutic agent" is meant especially any chemotherapeutic agent other than rapamycin or a derivative thereof. It includes but is not limited to,

i. an aromatase inhibitor,

ii. an antiestrogen, an anti-androgen (especially in the case of prostate cancer) or a gonadorelin agonist,

iii. a topoisomerase I inhibitor or a topoisomerase II inhibitor,

iv. a microtubule active agent, an alkylating agent, an antineoplastic antimetabolite or a platin compound,

v. a compound targeting/decreasing a protein or lipid kinase activity or a protein or lipid phosphatase activity, a further anti-angiogenic compound or a compound which induces cell differentiation processes,

vi. a bradykinin I receptor or an angiotensin II antagonist,

vii. a cyclooxygenase inhibitor, a bisphosphonate, a histone deacetylase inhibitor, a heparanase inhibitor (prevents heparan sulphate degradation), e.g. PI-88, a biological response modifier, preferably a lymphokine or interferons, e.g. interferon γ, an ubiquitination inhibitor, or an inhibitor which blocks anti-apoptotic pathways,

viii. an inhibitor of Ras oncogenic isoforms, e.g. H-Ras, K-Ras or N-Ras, or a famesyl transferase inhibitor, e.g. L-744,832 or DK8G557,

ix. a telomerase inhibitor, e.g. telomestatin,

x. a protease inhibitor, a matrix metalloprotelnase inhibitor, a methionine aminopeptidase inhibitor, e.g. bengamide or a derivative thereof, or a proteosome inhibitor, e.g. PS-341.

The term "aromatase inhibitor" as used herein relates to a compound which inhibits 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 atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole,

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 a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g. breast tumors.

The term "antiestrogen" as used herein relates to a compound which antagonizes 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 U.S. Pat. No. 4,659,516 or it can be administered, e.g., in the form as it is marketed, e.g. under the trademark FASLODE™. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g. breast tumors.

The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX™), which can be formulated, e.g. as disclosed in U.S. Pat. No. 4,636,505.

The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin is disclosed in U.S. Pat. No. 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 U.S. Pat. No. 5,843,901.

The term "topoisomerase I inhibitor" 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 inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, e.g. CAELYX™), daunorubicin, 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 agent" relates to microtubule [illegible] alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides and epothilones and derivatives thereof, e.g. epothilone B or a derivative thereof. Paclitaxel may be administered e.g. in the form as it is marketed, e.g. TAXOL™. 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 U.S. Pat. No. 5,010,099.

The term "alkylating agent" as used herein includes, but is not limited to cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel™). 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 "antineoplastic antimetabolite" includes, but is not limited to 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate. Capecitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark XELODA™. Gemcitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark GEMZAR™.

The term "platin compound" 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 targeting/decreasing a protein or lipid kinase activity or further anti-angiogenic compounds" as used herein includes, but is not limited to protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g. compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers), the vascular endothelial growth factor family of receptor tyrosine kinases (VEGFR), the platelet-derived growth factor-receptors (PDGFR), the fibroblast growth factor-receptors (FGFR), the insulin-like growth factor receptor 1 (IGF-1R), the Trk receptor tyrosine kinase family, the Axl receptor tyrosine kinase family, the Ret receptor tyrosine kinase, the Kit/SCFR receptor tyrosine kinase, members of the c-Abl family and their gene-fusion products (e.g. BCR-Abl), members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK or PI(3) kinase family, or of the PI(3)-kinase-related kinase family, and/or members of the cyclin-dependent kinase family (CDK) and anti-anglogenic compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition.

Compounds which target, decrease or inhibit the activity of VEGFR are especially compounds, proteins or antibodies which inhibit the VEGF receptor tyrosine kinase, inhibit a VEGF receptor or bind to VEGF, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by M. Prewett et al in Cancer Research 59 (1999) 5209-5218, by F. Yuan et [illegible]

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