

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 August 2002 (29.08.2002)

PCT

(10) International Publication Number
WO 02/066019 A2

- (51) International Patent Classification⁷: **A61K 31/00** [NZ/CH]; In den Kleematten 18, CH-4105 Biel-Benken (CH).
- (21) International Application Number: PCT/EP02/01714
- (22) International Filing Date: 18 February 2002 (18.02.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0104072.4 19 February 2001 (19.02.2001) GB
0124957.2 17 October 2001 (17.10.2001) GB
- (71) Applicant (for all designated States except AT, US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (71) Applicant (for AT only): **NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H.** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **LANE, Heidi** [CH/CH]; Lehenmattstr. 189, CH-4052 Basel (CH). **O'REILLY, Terence** [CA/CH]; Drahtzugstrasse 51, CH-4057 Basel (CH). **WOOD, Jeanette, Marjorie**
- (74) Agent: **BECKER, Konrad**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 02/066019 A2

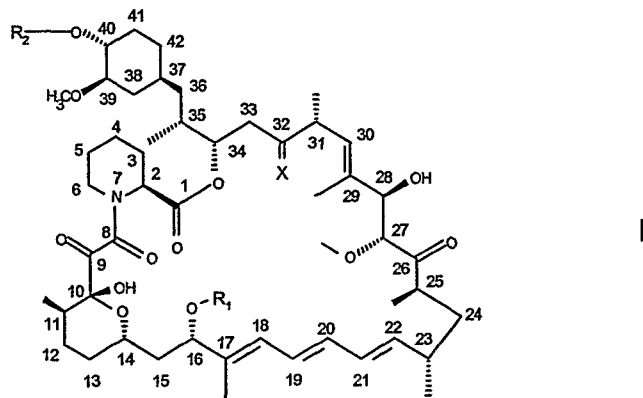
(54) Title: CANCER TREATMENT

(57) Abstract: Rapamycin derivatives have interesting effects in the treatment of solid tumours, optionally in combination with a chemotherapeutic agent.

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



wherein

R₁ is CH₃ or C₃₋₆alkynyl,

R₂ is H or -CH₂-CH₂-OH, and

X is =O, (H,H) or (H,OH)

provided that R₂ is other than H when X is =O and R₁ is CH₃.

Compounds of formula I are disclosed e.g. in WO 94/09010, WO 95/16691 or WO 96/41807, 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 WO 94/09010.

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 thereof, comprising administering to said subject a therapeutically effective amount of a compound of formula I.
- 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 (wherever 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 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 including 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 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.
- 1.7 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 USP 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, e.g. CCI779, ABT578 or a compound of formula I, e.g. Compound A, and b) a co-agent which is a chemotherapeutic agent selected from

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.