CASE 4-31671A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF

LANE ET AL.

INTERNATIONAL APPLICATION NO: PCT/EP02/01714

FILED: 18 FEBRUARY 2002

U.S. APPLICATION NO: Not Yet Known

35 USC §371 DATE: Herewith

FOR: TREATMENT OF SOLID TUMOURS WITH RAPAMYCIN DERIVATIVES

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir:

Prior to the examination of the above-referenced patent application, please enter the following preliminary amendments.

Amendments to the specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of the claims which begins on page 4 of this paper.

Remarks/Arguments begin on page 9 of this paper.

Amendments to the Specification:

A copy of the abstract is herein provided on the following separate sheet.

Abstract

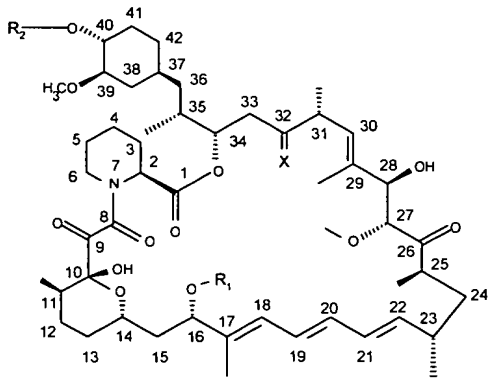
Rapamycin derivatives have interesting effects in the treatment of solid tumours, optionally in combination with a chemotherapeutic agent.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1. (currently amended) ~~Use of a compound of formula I~~ 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



I

wherein

R_1 is CH_3 or $C_{3\text{-}6}$alkynyl,

R_2 is H or $-CH_2-CH_2-OH$, 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[[,]].

~~in the preparation of a pharmaceutical composition for use in the treatment of solid tumors.~~

Claims 2-10. (cancelled)

Claim 11. (new) The method of claim 1, wherein said compound of formula I is administered concomitantly or sequentially with a co-agent which is a chemotherapeutic agent.

Claim 12. (new) The method of claim 11 wherein the co-agent is selected from the group consisting of

i. an aromatase inhibitor,

ii. an antiestrogen, an anti-androgen 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 1 receptor or an angiotensin II antagonist,

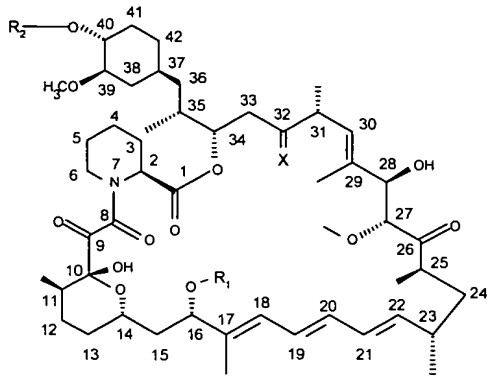
vii. a cyclooxygenase inhibitor, a bisphosphonate, a histone deacetylase inhibitor, a heparanase inhibitor, a biological response modifier, an ubiquitination inhibitor, or an inhibitor which blocks anti-apoptotic pathways,

viii. an inhibitor of Ras oncogenic isoforms,

ix. a telomerase inhibitor, and

x. a protease inhibitor, a matrix metalloproteinase inhibitor, a methionine aminopeptidase inhibitor, or a proteosome inhibitor.

Claim 13. (new) 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



I

wherein

R_1 is CH_3 or C_{3-6}alkynyl,

R_2 is H or $-CH_2-CH_2-OH$, 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.

Claim 14. (new) The method of claim 13, wherein said compound of formula I is administered concomitantly or sequentially with a co-agent which is a chemotherapeutic agent.

Claim 15. (new) The method of claim 14, wherein the co-agent is selected from the group consisting of

i. an aromatase inhibitor,

ii. an antiestrogen, an anti-androgen 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,

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