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(54) Title: COMPOUNDS USEFUL FOR THE TREATMENT OF CANCER, COMPOSITIONS THEREOF AND METHODS THEREWITH

(57) Abstract: The present invention generally relates to compounds and compositions useful for the modulation of ligase activity. The invention further relates to Compounds of the Invention, compositions thereof, and methods for treating or preventing cancer, a neoplastic disorder, acute or chronic renal failure, an inflammatory disorder, an immune disorder, a cardiovascular disease, an effect of aging or an infectious disease comprising administering an effective amount of a Compound of the Invention. The invention further relates to the use of a Compound of the Invention as a preservative of a cell, blood, tissue or an organ or as an agent to modulate stem cells.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/18905

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/35

US CL : 514/459

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)

U.S. : 514/459

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 practicable, search terms used)
WEST 2.1, STN, file cluster MEDICINE, and file REGISTRY

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2001/0044445 A1 (BAMAUNG et al.) 22 November 2001 (22.11.2001). See entire document.	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/18905

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

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

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim 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. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

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.: 1-3

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

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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

- I. Claims 1-3, drawn to a method for treating or preventing cancer or neoplastic disease and inhibiting the growth of a cancer cell with an effective amount of the compound of formula (I).
- II. Claim 4, drawn to a method for treating or preventing acute or chronic renal failure, inflammatory disease, an effect of aging, infectious disease, immune disorder or cardiovascular disease with an effective amount of the compound of formula (I).
- III. Claims 5-9 and 23 drawn to a method for treating or preventing a disease responsive to the modulation of ligase activity comprising administering an effective amount of the compound of formula (I) and a composition comprising the compound of formula (I) in a carrier.
- IV. Claim 10, drawn to a method for treating or preventing a disease responsive to the modulation of cellular p27/Kip1 levels comprising administering an effective amount of the compound of formula (I).
- V. Claims 11-13, drawn to a method for modulating cell growth comprising administering an effective amount of the compound of formula (I).
- VI. Claims 14-15, drawn to a method for preserving a cell, blood, organ or an organism comprising contacting blood, tissue or organ with an effective amount of the compound of formula (I).
- VII. Claims 16-21, drawn to a method for treating or preventing a side-effect of chemotherapy or radiation therapy comprising administering an effective amount of the compound of formula (I).
- VIII. Claim 22, drawn to a method for regulating or controlling the differentiation or maturation of a mammalian stem cell comprising administering an effective amount of the compound of formula (I).
- IX. Claim 24, drawn to a pharmaceutical composition for treating a disease associated with the modulation of a ligase comprising a compound of formula (II).

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions of group I and II have in common the technical feature of the compound of formula (I), however, the method of group I is drawn to treating or preventing cancer or neoplastic disease and inhibiting the growth of a cancer cell. the method of the group II invention is a method for treating or preventing acute or chronic renal failure, inflammatory disease, an effect of aging, infectious disease, immune disorder or cardiovascular disease. Since the treatment of acute or chronic renal failure, inflammatory disease, an effect of aging, infectious disease, immune disorder or cardiovascular disease is known to be treated with other agents such as COX-2 inhibitors, the determination of lack of unity is appropriate.

The inventions listed as Groups I and III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions of group I and III have in common the technical feature of the compound of formula (I), however, the method of group I is drawn to treating or preventing cancer or neoplastic disease and inhibiting the growth of a cancer cell. the method of the group III invention is a method for treating or preventing a disease responsive to the modulation of ligase activity. Since method of treating or preventing a disease responsive to the modulation of ligase activity is known to be treated with other agents such as anti-angiogenic agents, the determination of lack of unity is appropriate.

The inventions listed as Groups I and IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions of group I and IV have in common the technical feature of the compound of formula (I), however, the method of group I is drawn to treating or preventing cancer or neoplastic disease and inhibiting the growth of a cancer cell. The method of the group IV invention is a method for treating or preventing a disease responsive to the modulation of cellular p27/Kip1 levels. Since the treatment of a disease responsive to the modulation of cellular p27/Kip1 levels is known to be treated with other conventional cancer chemotherapeutic agents such as tamoxifen, the determination of lack of unity is appropriate.

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The inventions listed as Groups I and V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions of group I and V have in common the technical feature of the compound of formula (I), however, the method of group I is drawn to treating or preventing cancer or neoplastic disease and inhibiting the growth of a cancer cell. the method of the group V invention is a method for modulating cell growth. Since modulation of cell growth is known to be treated with other agents such as the Ras family of protéins, the determination of lack of unity is appropriate.

The inventions listed as Groups I and VI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions of group I and VI have in common the technical feature of the compound of formula (I), however, the method of group I is drawn to treating or preventing cancer or neoplastic disease and inhibiting the growth of a cancer cell. the method of the group VI invention is a method for preserving a cell, blood, organ or an organism. Since the preservation of a cell, blood, organ or organism is known to be accomplished with other agents such as anticoagulants and sodium citrate, the determination of lack of unity is appropriate.

The inventions listed as Groups I and VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions of group I and VII have in common the technical feature of the compound of formula (I), however, the method of group I is drawn to treating or preventing cancer or neoplastic disease and inhibiting the growth of a cancer cell. the method of the group VII invention is a method for treating or preventing a side-effect of chemotherapy or radiation therapy. Since the method for treating or preventing a side-effect of chemotherapy or radiation therapy is known to be treated with other agents such as Mesna (for cyclophosphamide-induced cystitis), the determination of lack of unity is appropriate.

The inventions listed as Groups I and VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions of group I and VIII have in common the technical feature of the compound of formula (I), however, the method of group I is drawn to treating or preventing cancer or neoplastic disease and inhibiting the growth of a cancer cell. the method of the group VIII invention is a method for regulating or controlling the differentiation or maturation of a mammalian stem cell. Since the treatment of acute or chronic renal failure, inflammatory disease, an effect of aging, infectious disease, immune disorder or cardiovascular disease is known to be treated with other agents such as human interferon-beta, the determination of lack of unity is appropriate.

The inventions listed as Groups I and IX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions of group I and IX have in common the technical feature of the compound of formula (I), however, the method of group I is drawn to treating or preventing cancer or neoplastic disease and inhibiting the growth of a cancer cell. the group IX invention is a composition or treating a disease associated with the modulation of a ligase comprising the compound of formula (II). Since the special technical feature of the group IX invention is not required for the group I invention, the determination of lack of unity is appropriate.