

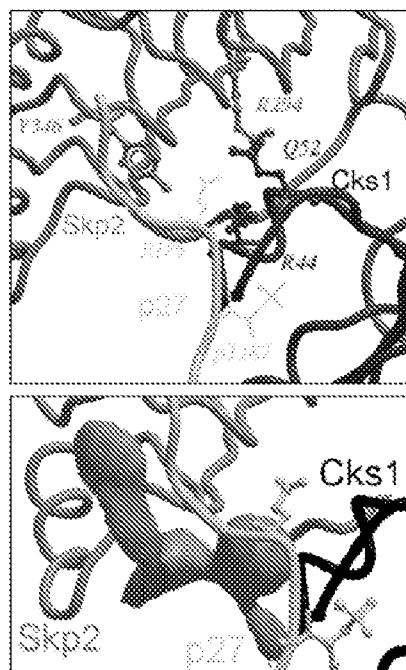


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[Continued on next page]

(54) Title: METHOD OF TREATING CANCER WITH MODULATORS OF SCFSkp2

A



(57) Abstract: The present invention relates to pharmaceutical compositions comprising a compound and a pharmaceutically acceptable carrier. The present invention is also directed to a method of treating cancer in a subject. Also disclosed are methods of inhibiting SCF-Skp2 activity and a method of identifying inhibitors of SCF-Skp2 activity. The ubiquitin proteasome system ("UPS") is essential for the turnover of almost all cellular proteins, maintaining homeostatic levels in normal cells while controlling levels of oncogenes and tumor suppressors in transformed cells.

**Published:**

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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19 June 2014

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/065256

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/426 (2014.01)

USPC - 514/369

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(8) - A61K 31/426; C07D 277/34, 277/36 (2014.01)

USPC - 514/369; 548/183

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

CPC - A61K 31/426; C07D 277/34, 277/36 (2014.02)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COULIBALY et al. Synthesis of New N,N'-Bis(5-arylidene-4-oxo-4,5-dihydrothiazolin-2-yl) piperazine Derivatives Under Microwave Irradiation and Preliminary Biological Evaluation. Sci Pharm. 80(4):825-836, 2012. [retrieved on 18 March 2014]. Retrieved from the Internet. <URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3528043/pdf/scipharm-2012-80-825.pdf> entire document	1, 4
A	US 2011/0269954 A1 (CHO et al) 03 November 2011 (03.11.2011) entire document	1, 4
A	WO 2004/006906 A2 (LEE et al) 22 January 2004 (22.01.2004) entire document	1, 4
A	US 2009/0054312 A1 (WOLF et al) 26 February 2009 (26.02.2009) entire document	1, 4
A	US 2004/0006112 A1 (ORCHARD et al) 08 January 2004 (08.01.2004) entire document	1, 4
A	US 6,201,127 B1 (COPP et al) 13 March 2001 (13.03.2001) entire document	1, 4

☐ Further documents are listed in the continuation of Box C.

* 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 application or patent 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

18 March 2014

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/065256

Box No. 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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 No. 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:

Claims 1 and 4 have been analyzed subject to the restriction that the claims read on the formula (I) as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a pharmaceutical composition comprising: a compound of formula (I); a stereoisomer, pharmaceutically acceptable salt, oxide, solvate, or ester thereof wherein ----- is a single bond; R is H; R1 is H; R2 is H; R3 is H; R4 is H; R5 is H; R6 is optional and absent; X is S; Y is S; and a pharmaceutically acceptable carrier.

<See Extra 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 additional fees, this Authority did not invite payment of additional fees.
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, 4

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/065256

<Continued from Box III: 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 need to be paid.

Group I+: Claims 1-6 are drawn to a pharmaceutical composition comprising: a compound of formula (I); a stereoisomer, pharmaceutically acceptable salt, oxide, solvate, or ester thereof.

Group II+: Claims 7-13 are drawn to a pharmaceutical composition comprising: a compound of formula (II); a stereoisomer, pharmaceutically acceptable salt, oxide, solvate, or ester thereof.

Group III: Claims 14-41 are drawn to pharmaceutical compositions comprising formula (III), (IV), and (V); and methods of treating cancer or inhibiting SCF-Skp2 activity comprising administering a compound of formula (I), (II), (III), (IV), or (V).

Group IV: Claims 42-47 are drawn to a method of identifying inhibitors of SCF-Skp2 activity.

Group V: Claims 48-52 are drawn to a method of inhibiting SCF-Skp2 activity in a subject.

The first invention of Group I+ is restricted to a pharmaceutical composition comprising: a compound of formula (I); a stereoisomer, pharmaceutically acceptable salt, oxide, solvate, or ester thereof wherein ----- is a single bond; R is H; R1 is H; R2 is H; R3 is H; R4 is H; R5 is H; R6 is optional and absent; X is S; Y is S; and a pharmaceutically acceptable carrier. It is believed that claims 1 and 4 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

The first invention of Group II+ is restricted to a pharmaceutical composition comprising: a compound of formula (II); a stereoisomer, pharmaceutically acceptable salt, oxide, solvate, or ester thereof wherein A is C; B is C; G is C; W is C; L1 is (1) absent; L2 is NH; L3 is (1) absent; L4 is (1) absent; L5 is (1) absent; R9 is H; R10 is H; R11 is H; R13 is H; R14 is H; R15 is H; R16 is H; R17 is H; R18 is H; and a pharmaceutically acceptable carrier in an exemplary election.

Applicant is invited to elect additional species of the formulas (I) and (II) to be searched in a specific combination for each formula by paying additional fees for each election. An exemplary election would be a pharmaceutical composition comprising: a compound of formula (I); a stereoisomer, pharmaceutically acceptable salt, oxide, solvate, or ester thereof wherein ----- is a double bond; R is H; R1 is H; R2 is H; R3 is H; R4 is H; R5 is H; R6 is optional and absent; X is S; Y is S; and a pharmaceutically acceptable carrier. Additional inventions will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ through 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 special technical features of Group I+, pharmaceutical compositions comprising a compound of formula (I), are not present in Groups II+ through V; the special technical features of Group II+, pharmaceutical compositions comprising a compound of formula (II), are not present in Groups I+ and III through V; the special technical features of Group III, pharmaceutical compositions comprising formula (III), (IV), and (V); and methods of treating cancer or inhibiting SCF-Skp2 activity, are not present in Groups I+, II+, IV, and V; the special technical features of Group IV, methods of identifying inhibitors of SCF-Skp2 activity, are not present in Groups I+ through III and V; and the special technical features of Group V, methods of inhibiting SCF-Skp2 activity in a subject comprising administering the compound under conditions effective to inhibit SCF-Skp2-mediated p27 degradation activity, are not present in Groups I+ through IV.

The Group I+ compounds of formula (I) do not share a significant structural element, requiring the selection of alternatives for the compound variables R, R1, R2, R3, R4, R5, R6, X, and Y.

The Group II+ compounds of formula (II) do not share a significant structural element, requiring the selection of alternatives for the compound variables A, B, G, W, L1, L2, L3, L4, L5, R9-R13, and R14-R18.

The Groups I+ through III share the technical features of pharmaceutical compositions comprising compounds of formula (I) or formula (II), a stereoisomer, pharmaceutically acceptable salt, oxide, solvate, or ester thereof; and a pharmaceutically acceptable carrier. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2011/0269954 A1 to Cho et al. teach a pharmaceutical composition comprising: a compound of formula (I); a stereoisomer, pharmaceutically acceptable salt, oxide, solvate, or ester thereof wherein ----- is a single or double bond; R is H; R1 is H; R2 is H; R3 is OR8; R4 is H; R5 is H; R8 is C1 alkyl; X is O; Y is S (see Paras. [0277]-[0278], Derivative 40 having the following formula was prepared as follows...Derivative 40 having the above formula, 5-(4-methoxybenzylidene)thiazolidine-2,4-dione); and a pharmaceutically acceptable carrier (see Para. [0074], pharmaceutical composition containing the derivative having formula (I) according to the present invention as an active ingredient may be manufactured by mixing the derivative with a pharmaceutically acceptable carrier).

Additionally, WO 2004/006906 A2 to Lee et al. teach a pharmaceutical composition comprising: a compound of formula (II); a stereoisomer, pharmaceutically acceptable salt, oxide, solvate, or ester thereof wherein A is C; B is C; G is C; W is C; L1 is (1) absent; L2 is NH; L3 is (1) absent; L4 is (1) absent; L5 is (1) absent; R9 is H; R10 is H; R11 is OC(O)R23; R12 is OR23; R13 is H; R14 is COOR23; R15 is H; R16 is H; R17 is halogen; R18 is H; R23 is H or C1-6 alkyl (see Pg. 175, Table 4-continued, Compound No. 10); and a pharmaceutically acceptable carrier (see Pg. 97 Right Col., 5. Pharmaceutical Compositions; Para. [1353], The sirtuin-modulating compounds described herein may be formulated in a conventional manner using one or more physiologically acceptable carriers).

<Continued in next Extra Sheet>

The Groups III through V share the technical features of methods of inhibiting SCF-Skp2 activity in a subject comprising selecting a subject in need of inhibiting Skp2-mediated p27 degradation; providing a compound which binds to and/or fits in a p27-binding interface of a Skp2-Cks 1 complex; and administering the compound to the selected subject under conditions effective to inhibit SCF-Skp2-mediated p27 degradation activity in the subject. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2009/0054312 A1 to Wolf et al. teach a method of inhibiting SCF-Skp2 activity in a subject comprising selecting a subject in need of inhibiting Skp2-mediated p27 degradation (see Para. [0004], deployed a screening assay to identify SMIPs, synthetic small molecules able to interfere with the depletion of the tumor suppressor p27 from human cancer cells); providing a compound which binds to and/or fits in a p27-binding interface of a Skp2-Cks 1 complex (see Para. [0004], ...screened 7368 chemical compounds from a variety of different libraries and identified 60 that show strong and reproducible SMIP activity. These compounds are useful for treating cancers and other proliferative diseases displaying p27 depletion; Para. [0159], SCFSKP2. Biochemical studies identified SKP2 as a subunit of a ubiquitin ligase complex, SCFSKP2, that mediates p27 degradation at the beginning of the S phase...and consists of five proteins: ... CKS1, and SKP2. SKP2 contains a so-called F-box which mediates binding to SKP1, and C-terminal leucine-rich repeats that recognize p27 in complex....); and administering the compound to the selected subject under conditions effective to inhibit SCF-Skp2-mediated p27 degradation activity in the subject (see Para. [0028], methods are provided for treating a cancer in a patient in need of such treatment comprising administering to the patient an effective amount of a composition comprising any of the aforementioned compounds).

Since none of the special technical features of the Groups I+ through V inventions are found in more than one of the inventions, unity is lacking.

<End Box III: Observations where unity of invention is lacking>