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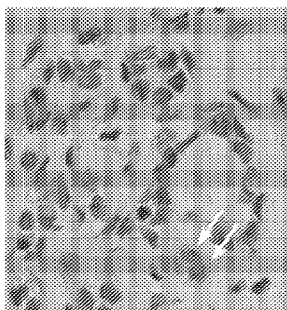
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21 September 2023 (21.09.2023)

(54) Title: COMPOUNDS AND METHODS FOR INHIBITING CANCERS OVER-EXPRESSING REPLICATION FACTOR C 40

(57) Abstract: Compounds and methods of inhibiting the expression and/or activity of Replication Factor C40 in cancer cells and of treating cancers expressing Replication Factor C 40 are described herein

A



A07-normal

FIG. 1



INTERNATIONAL SEARCH REPORT

International application No.

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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:

See extra sheet(s).

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, 30-34

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/US2023/011336

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - INV. - C07D 417/12; C07D 333/38; C07D 285/14; C07D 237/14; C07D 209/08 (2023.01)

ADD. - A61P 35/00 (2023.01)

CPC - INV. - C07D 417/12; C07D 333/38; C07D 285/14; C07D 237/14; C07D 209/08 (2023.05)

ADD. - A61P 35/00 (2023.05)

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)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,397,854 A (SIRCAR) 09 August 1983 (09.08.1983) entire document	1, 30
A	US 9,193,970 B1 (GUPTE) 24 November 2015 (24.11.2015) entire document	1, 30-34
A	US 2016/0075710 A1 (CHIESI FARMACEUTICI SPA) 17 March 2016 (17.03.2016) entire document	1, 30-34
A	US 2006/0035932 A1 (MURPHY et al.) 16 February 2006 (16.02.2006) entire document	1, 30-34
A	US 8,916,553 B2 (AUSTIN et al.) 23 December 2014 (23.12.2014) entire document	1, 30-34
A	PUBCHEM, Substance Record for SID 81037, Modify Date: 19 December 2011 [retrieved on 30 March 2023]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/81037 >. entire document	1, 30-34
A	PUBCHEM, Substance Record for SID 481485, Modify Date: 19 December 2011 [retrieved on 30 March 2023]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/481485 >. entire document	1, 30-34

☐ 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

"D" document cited by the applicant in the international application

"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

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Continued from Box No. III Observations where unity of invention is lacking

Claims 1 and 30-34 have been analyzed subject to the restriction that the claims read on a compound of shown Formula I including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms, wherein X is selected from the group consisting of aryl, wherein X is phenyl unsubstituted; and Y is alkyl, wherein Y is methyl unsubstituted; pharmaceutical compositions thereof; methods of inhibiting the expression and/or activity of RCF40 in a subject thereof; and methods of ameliorating or treating RCF40-mediated cancers in a subject thereof.

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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 1-4 and 30-34 (in part) are drawn to compounds of Formula I, pharmaceutical compositions thereof, methods of inhibiting the expression and/or activity of RCF40 in a subject thereof, and methods of ameliorating or treating RCF40-mediated cancers in a subject thereof.

Group II+: claims 5-10 and 30-34 (in part) are drawn to compounds of Formula II and III, pharmaceutical compositions thereof, methods of inhibiting the expression and/or activity of RCF40 in a subject thereof, and methods of ameliorating or treating RCF40-mediated cancers in a subject thereof.

Group III+: claims 11-15 and 30-34 (in part) are drawn to compounds of Formula IV, pharmaceutical compositions thereof, methods of inhibiting the expression and/or activity of RCF40 in a subject thereof, and methods of ameliorating or treating RCF40-mediated cancers in a subject thereof.

Group IV+: claims 16-19 and 30-34 (in part) are drawn to compounds of Formula V, pharmaceutical compositions thereof, methods of inhibiting the expression and/or activity of RCF40 in a subject thereof, and methods of ameliorating or treating RCF40-mediated cancers in a subject thereof.

Group V+: claims 20-25 and 30-34 (in part) are drawn to compounds of Formula VI and VII, pharmaceutical compositions thereof, methods of inhibiting the expression and/or activity of RCF40 in a subject thereof, and methods of ameliorating or treating RCF40-mediated cancers in a subject thereof.

Group VI+: claims 26-29 and 30-34 (in part) are drawn to compounds of Formula VIII, pharmaceutical compositions thereof, methods of inhibiting the expression and/or activity of RCF40 in a subject thereof, and methods of ameliorating or treating RCF40-mediated cancers in a subject thereof.

The first invention of Group I+ is restricted to a compound of shown Formula I including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms, wherein X is selected from the group consisting of aryl, wherein X is phenyl unsubstituted; and Y is alkyl, wherein Y is methyl unsubstituted; pharmaceutical compositions thereof; methods of inhibiting the expression and/or activity of RCF40 in a subject thereof; and methods of ameliorating or treating RCF40-mediated cancers in a subject thereof. It is believed that claims 1 and 30-34 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 compound of shown Formula II including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms, wherein A is selected from the group consisting of CR'; B is selected from the group consisting of CR'; D is selected from the group consisting of CR'; E at each instance is independently selected from the group consisting of C; R' at each instance is independently selected from the group consisting of H; R1 and R1' are each individually selected from the group consisting of H; R2 and R2' are each individually selected from the group consisting of H; and R3 is selected from the group consisting of H; and a compound of Formula III thereof.

The first invention of Group III+ is restricted to a compound of shown Formula IV including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms, wherein A is selected from the group consisting of CR'; B is selected from the group consisting of CR'; D is selected from the group consisting of CR'; E at each instance is independently selected from the group consisting of CR'; R' at each instance is independently selected from the group consisting of H; R1 and R1 are each individually selected from the group consisting of H; R2 and R2' are each individually selected from the group consisting of H; and R3 is selected from the group consisting of H.

The first invention of Group IV+ is restricted to a compound of shown Formula V including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms, wherein R6, R7, R8, R9, R10, and R11 are each individually selected from the group consisting of H; R12 is selected from the group consisting of H; and n is an integer selected from the group consisting of 0.

The first invention of Group V+ is restricted to a compound of shown Formula VI including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms, wherein R6, R7, R8, R9, and R10 are each individually selected from the group consisting of H; R12 is selected from the group consisting of H; R15 is selected from the group consisting of H; and n is an integer selected from the group consisting of 0; and a compound of Formula VII thereof.

The first invention of Group VI+ is restricted to a compound of shown Formula VIII including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms, wherein G each instance is individually selected from the group consisting of CH; J is selected from the group consisting of CH; R' is selected from the group consisting of H; R1, R1', R2, R2', and R3 are each individually selected from the group consisting of H; R13, R14, R15, and R16 are each individually selected from the group consisting of H; and m and n are each individually selected from an integer selected from the group consisting of 0.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of shown Formula I including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms, wherein X is selected from the group consisting of aryl, wherein X is phenyl unsubstituted; and Y is alkyl, wherein Y is ethyl unsubstituted; pharmaceutical compositions thereof; methods of inhibiting the expression and/or activity of RCF40 in a subject thereof; and methods of ameliorating or treating RCF40-mediated cancers in a subject thereof. Additional formula(e) 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+ to VI+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT

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Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, compounds of Formula I, are not present in Groups II+ to VI+; the special technical features of Group II+, compounds of Formula II and III, are not present in Groups I+ and III+ to VI+; the special technical features of Group III+, compounds of Formula IV, are not present in Groups I+, II+, and IV+ to VI+; the special technical features of Group IV+, compounds of Formula V, are not present in Groups I+ to III+, V+ and VI+; the special technical features of Group V+, compounds of Formula VI and VII, are not present in Groups I+ to IV+ and VI+; and the special technical features of Group VI+, compounds of Formula VIII, are not present in Groups I+ to V+.

The Groups I+ to VI+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables X, Y, A, B, D, E, R1, R1', R2, R2', R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, n, R13, R14, R15, R16, G, J, and m, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ to VI+ were considered to share the technical features of a compound of the core structure of Formula I including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms; a compound of the core structure of Formula II including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms; a compound of the core structure of Formula III including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms; a compound of the core structure of Formula IV including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms; a compound of the core structure of Formula V including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms; a compound of the core structure of Formula VI including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms; a compound of the core structure of Formula VII including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms; a pharmaceutical composition comprising a compound or an enantiomer, diastereomer, hydrate, solvate, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient; a method of inhibiting the expression and/or activity of RCF40 in a subject, comprising administering to the subject a compound or an enantiomer, diastereomer, hydrate, solvate, or a pharmaceutically acceptable salt thereof, wherein the activity of RCF40 activity is inhibited in the subject; and a method of ameliorating or treating RCF40-mediated cancers in a subject, comprising administering to the subject an effective amount of a compound or an enantiomer, diastereomer, hydrate, solvate, or a pharmaceutically acceptable salt thereof, wherein the growth of cancer cells is inhibited in a subject, these shared technical features do not represent a contribution over the prior art as disclosed by US 4,397,854 A to Sircar, US 2006/0035932 A1 to Murphy et al., US 8,916,553 B2 to Austin et al., PubChem SID 81037, PubChem SID 481485, and US 9,193,970 B1 to Gupte.

US 4,397,854 A to Sircar teaches a compound of the core structure of Formula I including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms (Claim 5, 2-methyl-6-phenyl-3(2H)-pyridazinone).

US 2006/0035932 A1 to Murphy et al. teach a compound of the core structure of Formula II including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms (Pg. 34, Table II-continued, third shown compound (see shown structure)); and a compound of the core structure of Formula III including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms (Pg. 34, Table II-continued, third shown compound (see shown structure)).

US 8,916,553 B2 to Austin et al. teach a compound of the core structure of Formula IV including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms (Col. 115, Table 7, Ex. No. 71, see shown structure); and a compound of the core structure of Formula VIII including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms (Col. 95, Table 7, Ex. No. 2, see shown structure).

PubChem SID 81037 teaches a compound of the core structure of Formula V including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms (Pg. 2, see shown structure).

PubChem SID 481485 teaches a compound of the core structure of Formula VI including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms (Pg. 2, see shown structure); and a compound of the core structure of Formula VII including all pharmaceutically acceptable salts, crystalline forms, stereoisomers, prodrugs, and amorphous forms (Pg. 2, see shown structure).

US 9,193,970 B1 to Gupte teaches a pharmaceutical composition comprising a compound or an enantiomer, diastereomer, hydrate, solvate, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient (Claim 1, pharmaceutical composition for use in prophylaxis and/or therapy of cancer, the composition comprising a pharmaceutically acceptable carrier and an isolated polynucleotide); a method of inhibiting the expression and/or activity of RCF40 in a subject, comprising administering to the subject a compound or an enantiomer, diastereomer, hydrate, solvate, or a pharmaceutically acceptable salt thereof, wherein the activity of RCF40 activity is inhibited in the subject (Col. 3, Lns. 30-32, methods for the treatment of breast cancer and/or the reduction of risk for breast cancer by modulating RFC40; Col. 5, Lns. 16-19, method is provided for prophylaxis and or therapy of cancer, including breast cancer, in a mammal comprising administering to said mammal the above composition(s); Col. 19, Lns. 33-35, The pharmaceutical or therapeutic compositions may further include an effective amount of the RFC40 inhibitory agent or compound); and a method of ameliorating or treating RCF40-mediated cancers in a subject, comprising administering to the subject an effective amount of a compound or an enantiomer, diastereomer, hydrate, solvate, or a pharmaceutically acceptable salt thereof, wherein the growth of cancer cells is inhibited in a subject (Col. 5, Lns. 16-19, method is provided for prophylaxis and or therapy of cancer, including breast cancer, in a mammal comprising administering to said mammal the above composition(s); Col. 19, Lns. 33-35, The pharmaceutical or therapeutic compositions may further include an effective amount of the RFC40 inhibitory agent or compound).

The inventions listed in Groups I+ to VI+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.