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(81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,

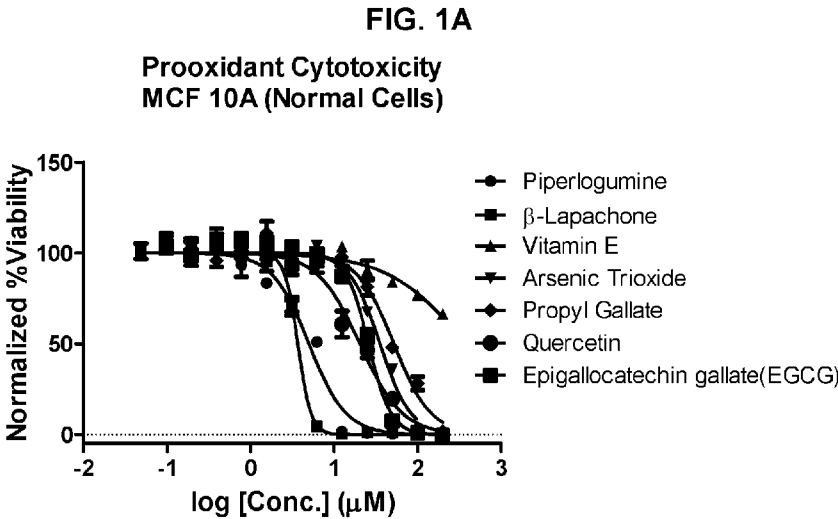
CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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(88) **Date of publication of the international search report:**
19 September 2024 (19.09.2024)

(54) **Title:** COMBINATION THERAPY FOR CANCER USING ROS-ACTIVATED PRODRUGS AND ROS-AMPLIFYING THERAPEUTICS



(57) **Abstract:** Described herein is an anticancer and anti-inflammatory combination therapy comprising one or more antineoplastic agents and one or more pro-oxidants. In one embodiment, the antineoplastic agent is not active in the absence of the pro-oxidant. In another embodiment, the pro-oxidant is administered prior to the antineoplastic agent to induce targeted activity of the antineoplastic agent.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 24/11722

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/015, A61K 31/03, A61K 31/13, A61K 31/69 (2024.01)
ADD. F24F 7/003 (2024.01)

CPC - INV. A61K 31/015, A61K 31/03, A61K 31/13, A61K 31/69

ADD. F24F 7/003

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 data base consulted during the international search (name of data base 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.
A	US 9,108,989 B2 (Infinity Pharmaceuticals, Inc.), 18 August 2015 (18.08.2015), entire document, especially col 3, ln 11-58; col 4, ln 14-15; col 9, ln 20-22; col 183, ln 19-24; col 186, ln 4-5	1-3, 5, 7-9, 11-13
A	US 2013/0045949 A1 (Peng et al.), 21 February 2013 (21.02.2013), entire document, especially para[0005]-[0014], [0263], [0270], [0295], [0366]	1-3, 5, 7-9, 11-13
A	Bannerman et al., "Preclinical evaluation of the antitumor activity of bortezomib in combination with vitamin C or with epigallocatechin gallate, a component of green tea", 13 March 2011 (13.03.2011), Cancer Chemother Pharmacol, 68, Pages 1145-1154, entire document, especially page 1145, col 1, para 1; page 1148, col 1, para 2	1-3, 5, 7-9, 11-13
A	Abgelella et al., "Oxidative Stress in the Tumor Microenvironment and Its Relevance to Cancer Immunotherapy", 27 February 2021 (27.02.2021), Cancers, 13(5), 986, Pages 1-33, entire document, especially page 9, para 2; page 13, para 2	1-3, 5, 7-9, 11-13
A	Campbell et al., "Antimyeloma effects of arsenic trioxide are enhanced by melphalan, bortezomib and ascorbic acid", 29 June 2007 (29.06.2007), British Journal of Haematology, Volume 138, Issue 4, Pages 467-478, entire document, especially page 467, col 2, para 2; page 468, col 1, para 1	1-3, 5, 7-9, 11-13

☐ 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

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 24/11722

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 supplemental box----

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.:
1-3, 5, 7-9, 11-13

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/US 24/11722

Box III: lack of unity

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 searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-13 and 27 are directed to a combination therapeutic comprising: a therapeutically effective amount of one or more antineoplastic agents, or pharmaceutically acceptable salts or esters thereof, and a therapeutically effective amount of one or more pro-oxidants, or a pharmaceutically acceptable salts or esters thereof. Claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a combination therapeutic comprising: a therapeutically effective amount of one or more antineoplastic agents, or pharmaceutically acceptable salts or esters thereof, wherein the antineoplastic agent has a structure as seen in instant claim 3 wherein X, at each occurrence, is independently halo; R1, at each occurrence, is independently hydrogen; R2 is BH(OR1b); R1b is hydrogen; and a therapeutically effective amount of one or more pro-oxidants, wherein the pro-oxidant is vitamin C as listed in instant claim 11, or a pharmaceutically acceptable salts or esters thereof. It is believed that claims 1-3, 5, 7-9, and 11-13 read on this first named invention, and thus these claims will be searched without fee. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass 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. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a combination therapeutic comprising: a therapeutically effective amount of one or more antineoplastic agents, or pharmaceutically acceptable salts or esters thereof, wherein the antineoplastic agent has a structure as seen in instant claim 3 wherein X, at each occurrence, is independently halo; R1, at each occurrence, is independently hydrogen; R2 is BH(OR1b); R1b is C1 alkyl; and a therapeutically effective amount of one or more pro-oxidants, wherein the pro-oxidant is vitamin C as listed in instant claim 11, or a pharmaceutically acceptable salts or esters thereof (i.e., claims 1-3, 5, 7-9, 11-13).

Group II: Claims 14-26 and 28 are directed to a method for treating a disease or disorder, the method comprising: sequentially or simultaneously administering to a subject in need thereof a therapeutically effective amount of one or more antineoplastic agents, or pharmaceutically acceptable salts or esters thereof, and a therapeutically effective amount of one or more pro-oxidants, or pharmaceutically acceptable salts or esters thereof; and repeating the administration until the disease or disorder is treated, ameliorated, or symptoms are reduced.

The group of inventions listed above 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:

Special Technical Features:

Each invention in Group I+ includes the technical feature of a combination therapeutic comprising: a therapeutically effective amount of one or more unique antineoplastic agents, or pharmaceutically acceptable salts or esters thereof, and a therapeutically effective amount of one or more unique pro-oxidants, or a pharmaceutically acceptable salts or esters thereof, which is not required by any other invention of Group I+.

Group II requires a method for treating a disease or disorder, the method comprising: sequentially or simultaneously administering to a subject in need thereof a therapeutically effective amount of one or more antineoplastic agents, or pharmaceutically acceptable salts or esters thereof, and a therapeutically effective amount of one or more pro-oxidants, or pharmaceutically acceptable salts or esters thereof; and repeating the administration until the disease or disorder is treated, ameliorated, or symptoms are reduced, which is not required by Group I+.

Common Technical Features:

The inventions of Groups I+ and II share the technical feature of a combination therapeutic comprising: a therapeutically effective amount of one or more antineoplastic agents, or pharmaceutically acceptable salts or esters thereof, and a therapeutically effective amount of one or more pro-oxidants, or a pharmaceutically acceptable salts or esters thereof.

These shared technical features, however, do not provide a contribution over the prior art as being anticipated by a document entitled "Preclinical evaluation of the antitumor activity of bortezomib in combination with vitamin C or with epigallocatechin gallate, a component of green tea" to Bannerman et al. (hereinafter 'Bannerman'). Bannerman teaches a combination therapeutic comprising: a therapeutically effective amount of one or more antineoplastic agents, or pharmaceutically acceptable salts or esters thereof wherein the antineoplastic agent is bortezomib; and a therapeutically effective amount of one or more pro-oxidants, or pharmaceutically acceptable salts or esters thereof, wherein the pro-oxidant is vitamin C as listed in instant claim 11 (page 1145, col 1, para 1, 'Purpose: to investigate whether clinically relevant levels of...vitamin C (ascorbic acid) could antagonize bortezomib antitumor activity in CWR22 human prostate xenograft tumors'; page 1148, col 1, para 2, 'For the vitamin C studies, mice were dosed with vehicle (0.9% saline IV BIW)...a combination of ascorbic acid (40 or 500 mg/kg PO QD) and bortezomib (0.8 mg/kg IV BIW) for 22 days.').

As said compound was known in the art, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ and II. The inventions of Group I+ and II thus lack unity under PCT Rule 13.