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(88) Date of publication of the international search report:
27 December 2012

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(54) Title: ANTI-VIRAL COMBINATION THERAPY

(57) Abstract: The present invention provides methods and compounds for treating viral infections using combinations modulators of an HCV-associated component and modulators of host cell enzymes. The present invention also provides methods and compounds for treating viral infections using combinations of modulators of host cell enzymes and other agents that work, at least in part by modulating host factors.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/32567

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/18; A61K 38/21; A61K 39/395; A61K 39/42 (2012.01)
USPC - 514/4.3
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)
USPC: 514/4.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/158.1, 424/161.1, 424/189.1, 424/85.4 (keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar
Search Terms Used: Acetyl coa carboxylase, HCV, TOFA, boceprevir, pegasys, taribavirin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Kapadia et al. 'Hepatitis C virus RNA replication is regulated by host geranylgeranylation and fatty acids' PNAS vol 102 pg 2561-2566; 15 February 2005 (15.02.2005) pg 2563, col 2, para 2, Fig. 4A	1-10, 54-56
Y	US 2010/0280099 A1 (Elmen) 04 November 2010 (04.11.2010) para [0007], [0047], [0092], [0485]	1-10, 54-56
Y	US 2009/0239830 A1 (Munger et al.) 24 September 2009 (24.09.2009) para [0010]-[0011], [0190], [0192]	5-7, 54-56/5-7
Y	US 2010/0143301 A1 (Desai et al.) 10 June 2010 (10.06.2010) para [0010], [0194], [0199]-[0200]	9-10, 54-56
Y	Yang et al. 'Fatty Acid Synthase Is Upregulated during HCV Infection and Regulates HCV Entry and Production' Hepatology vol 48 pg 1396-1403; November 2008 (11.2008) whole doc.	1-10, 54-56

☐ 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	Date of mailing of the international search report
14 September 2012 (14.09.2012)	27 SEP 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/32567

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:
- Please see extra sheet for continuation -

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.:
1-10 and 54-56

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 12/32567

Continuation of:
Box NO III. Observations where unity of invention is lacking

Group I+: claims 1-10 and 54-77, drawn to a method of treating or preventing HCV infection comprising administering to a subject in need thereof a therapeutically effective amount of (i) a compound that is an inhibitor of acetyl-CoA carboxylase (ACC) or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug. The modulator of an HCV-associated component is selected from HCV protease inhibitors, HCV NS3 inhibitors, HCV NS4B inhibitors, HCV NS5A inhibitors, HCV NS5B inhibitors, HCV viral ion channel forming protein inhibitors, HCV IRES inhibitors, HCV entry inhibitors, cyclosporin inhibitors, and modulator of miR-122. The first invention is restricted to HCV protease inhibitors (Claims 1-10 and 54-56). Should an additional fee(s) be paid, Applicant is invited to elect an additional class(es) of modulator of HCV-associated component to be searched. The exact claims searched will depend on Applicant's election.

Group II+: claims 11-14 and 54-77, drawn to a method of treating or preventing HCV infection comprising administering to a subject in need thereof a therapeutically effective amount of (i) a compound that is a modulator of a host cell target or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug. The modulator of an HCV-associated component is selected from HCV protease inhibitors, HCV NS3 inhibitors, HCV NS4B inhibitors, HCV NS5A inhibitors, HCV NS5B inhibitors, HCV viral ion channel forming protein inhibitors, HCV IRES inhibitors, HCV entry inhibitors, cyclosporin inhibitors, and modulator of miR-122. The first invention is restricted to HCV protease inhibitors. Should an additional fee(s) be paid, Applicant is invited to elect an additional class(es) of modulator of HCV-associated component to be searched. The exact claims searched will depend on Applicant's election.

Group III+: claims 15-22 and 54-77, drawn to a method of treating or preventing HCV infection comprising administering to a subject in need thereof a therapeutically effective amount of (i) a compound that is an inhibitor of an acyl-CoA:cholesterol acyl-transferase (ACAT) or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug. The modulator of an HCV-associated component is selected from HCV protease inhibitors, HCV NS3 inhibitors, HCV NS4B inhibitors, HCV NS5A inhibitors, HCV NS5B inhibitors, HCV viral ion channel forming protein inhibitors, HCV IRES inhibitors, HCV entry inhibitors, cyclosporin inhibitors, and modulator of miR-122. The first invention is restricted to HCV protease inhibitors. Should an additional fee(s) be paid, Applicant is invited to elect an additional class(es) of modulator of HCV-associated component to be searched. The exact claims searched will depend on Applicant's election.

Group IV: claims 23-28 and 54-77, drawn to a method of treating or preventing HCV infection comprising administering to a subject in need thereof a therapeutically effective amount of (i) a compound that is an inhibitor of a long-chain acyl-CoA synthetase (ACSL) or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug.

Group V: claims 29-33 and 54-77, drawn to a method of treating or preventing HCV infection comprising administering to a subject in need thereof a therapeutically effective amount of (i) a compound that is an inhibitor of an elongase (ELOVL) or a prod rug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug.

Group VI+: claims 34-38 and 54-77, drawn to a method of treating or preventing HCV infection comprising administering to a subject in need thereof a therapeutically effective amount of (i) a compound that is an inhibitor of fatty acid synthase (F AS) or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug. The modulator of an HCV-associated component is selected from HCV protease inhibitors, HCV NS3 inhibitors, HCV NS4B inhibitors, HCV NS5A inhibitors, HCV NS5B inhibitors, HCV viral ion channel forming protein inhibitors, HCV IRES inhibitors, HCV entry inhibitors, cyclosporin inhibitors, and modulator of miR-122. The first invention is restricted to HCV protease inhibitors. Should an additional fee(s) be paid, Applicant is invited to elect an additional class(es) of modulator of HCV-associated component to be searched. The exact claims searched will depend on Applicant's election.

Group VII+: claims 39-43 and 54-77, drawn to a method of treating or preventing HCV infection comprising administering to a subject in need thereof a therapeutically effective amount of (i) a compound that is an inhibitor of HMG-CoA reductase or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug. The modulator of an HCV-associated component is selected from HCV protease inhibitors, HCV NS3 inhibitors, HCV NS4B inhibitors, HCV NS5A inhibitors, HCV NS5B inhibitors, HCV viral ion channel forming protein inhibitors, HCV IRES inhibitors, HCV entry inhibitors, cyclosporin inhibitors, and modulator of miR-122. The first invention is restricted to HCV protease inhibitors. Should an additional fee(s) be paid, Applicant is invited to elect an additional class(es) of modulator of HCV-associated component to be searched. The exact claims searched will depend on Applicant's election.

Group VIII: claims 44-48 and 54-77, drawn to a method of treating or preventing HCV infection comprising administering to a subject in need thereof a therapeutically effective amount of (i) a compound that is an inhibitor of lipid droplet formation or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug.

Group IX: claims 49-77, drawn to a method of treating or preventing HCV infection comprising administering to a subject in need thereof a therapeutically effective amount of (i) a compound that is an inhibitor of serine palmitoyl transferase (SPT) or a prod rug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug.

- Please see extra sheet for continuation -

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/32567

Continuation of:
Box NO III. Observations where unity of invention is lacking

The inventions listed as Groups I+ through 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 Groups I+-IX comprise distinct inventive concepts for treating or preventing HCV infection comprising inhibitors for host cell targets selected from ACC, ACAT, ACSL, ELOVL, FAS, HMG-CoA reductase, lipid droplet formation, and SPT, respetively, as outlined above.

The inventions of Groups I+-IX share the technical feature of a method of treating or preventing HCV infection comprising administering to a subject in need thereof a therapeutically effective amount of (i) a compound that is a modulator of a host cell target or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2010/0280099 A1 (Elmen). Elmen discloses Claim 15, a method of treating or preventing HCV infection (para [0007]) comprising administering to a subject in need thereof a therapeutically effective amount (para [0485]) of (i) a compound that is an inhibitor of an acyl-CoA:cholesterol acyl-transferase (ACAT) or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug (para [0092], ACAT2) and (ii) a compound that is a modulator of an HCV-associated component or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug (para [0047], ribavirin). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Groups I+ through IX is the specific modulator of an HCV-associated components recited therein. The inventions do not share a special technical feature, because Elmen teaches a specific modulator of an HCV-associated component that is a modulator of miR-122 (para [0010]-[0011]). Without a shared special technical feature, the inventions lack unity with one another.

Another special technical feature of the inventions listed as Groups I+ is a compound that is an inhibitor of acetyl-CoA carboxylase (ACC) or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug. However, this shared technical feature does not represent a contribution over prior art as being anticipated by the article entitled 'Hepatitis C virus RNA replication is regulated by host geranylgeranylation and fatty acids' by Kapadia et al. (hereinafter 'Kapadia'). Kapadia teaches a method of treating or preventing HCV infection comprising administering to a subject in need thereof a compound that is an inhibitor of acetyl-CoA carboxylase (ACC) (pg 2563, col 2, para 2, to determine whether the fatty acid biosynthetic pathway plays a role in regulating HCV replication, we inhibited the enzyme acetyl-CoA carboxylase by using TOFA. Treatment of Sfil cells with TOFA resulted in a 3-fold inhibition of HCV RNA replication (Fig. 4A)). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Groups VI+ is a compound that is an inhibitor of fatty acid synthase (FAS) or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug. However, this shared technical feature does not represent a contribution over prior art as being anticipated by the article entitled 'Fatty Acid Synthase Is Upregulated during HCV Infection and Regulates HCV Entry and Production' by Yang et al. (hereinafter 'Yang'). Yang teaches a method of treating or preventing HCV infection comprising administering to a subject in need thereof a compound that is an inhibitor of fatty acid synthase (FAS) (abstract, blocking fatty acid synthase activity by a pharmacological inhibitor C75 led to decreased HCV production. Reduction of fatty acid synthase by RNA interference (RNAi) suppressed viral replication in both replicon and infection systems, see Fig. 3). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Groups VII+ is a compound that is an inhibitor of HMG-CoA reductase or a prodrug thereof, or pharmaceutically acceptable salt or ester of said compound or prodrug. However, this shared technical feature does not represent a contribution over prior art as being anticipated by Kapadia. Kapadia teaches a method of treating or preventing HCV infection comprising administering to a subject in need thereof a compound that is an inhibitor of HMG-CoA reductase (pg 2563, col 1, para 2, we also treated Sfil cells with L-659,699 and ZA, which are specific inhibitors of HMG-CoA synthase and squalene synthase, respectively. Treatment of Sfil cells with L-659,699 also inhibited HCV RNA replication in a dose-dependent manner (Fig. 2B) without any detectable effect on cell-cycle progression (data not shown).). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I+ through IX therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.