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(54) Title: PROTEOSTASIS REGULATORS

(57) Abstract: The present invention is directed to compounds of Formulae (I), (II), (III), (IV), (V), (VI), (VII), and (VIII), pharmaceutical compositions thereof and methods of use thereof in the treatment of conditions associated with a dysfunction in proteostasis.



WO 2012/078902 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/63992

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 43/90; A01N 43/42; A61K 31/44 (2012.01) USPC - 514/264.1 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) -A01N 43/90; A01N 43/42; A61K 31/44 (2012.01) USPC -514/264.1 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 514/300, 302; 544/279; 546/115, 122-123 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWest, Google Patents, Google Scholar, WIPO (proteostasis, dysfunction, formula, phthalazinedione, homeostasis, function, dihydropyridine, transmembrane, cystic, protein, gain, loss, tau, phthalazine, cancer, tumor, dione, parkinson, huntington, alzheimer, regulator, chaperone, naphthyl, thienyl, piperazine, pyridine, tau, huntingtin, dismutase, t														
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X --- Y</td> <td>US 2007/0112015 A1 (HURT, et al.) 17 May 2007 (17.05.2007) entire document, especially para[0023], [0043], [0058]-[0059], [0067], [0074], [0103], [0108], [0267], [0317]</td> <td>1-13 ----- 57, 59, 62, 66, 70/59,62,66, 71/59,62,66, 72-73, 75, 76/59,62,66, 77-78</td> </tr> <tr> <td>Y</td> <td>US 2010/0086531 A1 (HENRY, et al.) 08 April 2010 (08.04.2010) entire document, especially para[0020], [0030], [0096], [0106], [0110]-[0111], [0113].</td> <td>57, 59, 62, 66, 70/59,62,66, 71/59,62,66, 72-73, 75, 76/59,62,66 and 77-78</td> </tr> <tr> <td>A</td> <td>PubChem compound CID 3149274 (Create date 2005-06010) (retrieved from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3149274 on 10 August 2012)</td> <td>1</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X --- Y	US 2007/0112015 A1 (HURT, et al.) 17 May 2007 (17.05.2007) entire document, especially para[0023], [0043], [0058]-[0059], [0067], [0074], [0103], [0108], [0267], [0317]	1-13 ----- 57, 59, 62, 66, 70/59,62,66, 71/59,62,66, 72-73, 75, 76/59,62,66, 77-78	Y	US 2010/0086531 A1 (HENRY, et al.) 08 April 2010 (08.04.2010) entire document, especially para[0020], [0030], [0096], [0106], [0110]-[0111], [0113].	57, 59, 62, 66, 70/59,62,66, 71/59,62,66, 72-73, 75, 76/59,62,66 and 77-78	A	PubChem compound CID 3149274 (Create date 2005-06010) (retrieved from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3149274 on 10 August 2012)	1
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☐ 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 08 August 2012 (08.08.2012)		Date of mailing of the international search report 23 AUG 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 11/63992

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.: 56, 74
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--

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.:
1-13, 57, 59, 62, 66, 70-73, 75-78

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 11/63992

Continuation of:

Box NO III. Observations where unity of invention is lacking

Group I+: claims 1-19, 52-55, 57-59, 61-68, 70-73 and 75-79, drawn to a compound having the formula (I), (II), (VI) and (VII). The first invention is restricted to the first compound of Claim 13. Should an additional fee(s) be paid, Applicant is invited to elect an additional compound(s) to be searched. The exact claims searched will depend on Applicant's election.

[Claims 14-19, 52-55, 58, 60-61, 63-65, 67-68 and 79 are excluded from Group I, because they are drawn to a non-elected subject matter.]

Group II: claims 20-47, 58-59, 69, 70-73 and 76-79, drawn to a compound having the formula (III), (IV) and (VIII).

Group III: claims 20, 48-51, 58-60, 70-73 and 76-79, drawn to a compound having the formula (V).

The inventions listed as Groups I+ through 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 Groups I+-III do not share a single general inventive concept. Formula I and VII of Group I+ share a common pharmacophore. Formula II and VI of Group I+ share a common pharmacophore. Formula III, IV and VIII of Group II share a common pharmacophore. However, no significant structural similarities can readily be ascertained between Formula I and Formula II of Group I+. In addition, no significant structural similarities can readily be ascertained among formula I and II of Group I+; Formula III, IV and VIII of Group II, and Formula V of Group III. Without a shared special technical feature, the inventions lack unity with one another.

The inventions of Group I+-III share the technical feature of a proteostasis regulator. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2009/0203605 A1 to Segatori et al. (hereinafter 'Segatori'). Segatori discloses methods for treating conditions characterized by dysfunction in protein homeostasis in a patient in need thereof comprising administering to the patient a proteostasis regulator in an amount and dosing schedule effective to improve or restore protein homeostasis. The proteostasis regulator can act via a cellular mechanism that upregulates signaling via a heat shock response pathway and/or an unfolded protein response pathway (para [0012] and [0020]). 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.

The inventions of Group I+ share the technical feature of a compound having formula (I) and (VII). However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2007/0112015 A1 to Hurt et al. (hereinafter 'Hurt'). Hurt discloses a compound having formula (VII), wherein R1 is selected from optionally substituted aryl, R2a is selected from C(O)OR5 wherein R5 is selected from optionally substituted C3-C10 cycloalkyl, R2b is selected from optionally substituted C1-C10 alkyl, R4a and R4b at each occurrence are each independently selected from hydrogen, R22 at each occurrence is independently selected from optionally substituted aryl, Y at each occurrence is selected from C(R4a)(R4b) wherein R4a and R4b are each independently selected from hydrogen (Fig. 1, col 1, 6th compound). 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.

The inventions of Group I+ share the technical feature of a compound having formula (II) and (VI). However, this shared technical feature does not represent a contribution over prior art as being anticipated by PubChem compound CD 3149274 (first created 2005-08-01) (retrieved from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3149274&loc=ec_rcs on 06 Marh 2012). CID 3149274 is a compound having claimed formula (VI) wherein R6a and R6b at each occurrence are each independently selected from hydrogen, R21a is selected from optionally substituted aryl, R21b is selected from hydrogen. 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 III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.