

(10) International Publication Number
WO 2015/116663 A1(43) International Publication Date
6 August 2015 (06.08.2015)

(51) International Patent Classification:

C07D 417/14 (2006.01) A61P 25/28 (2006.01)
A61K 31/4045 (2006.01)

(21) International Application Number:

PCT/US2015/013263

(22) International Filing Date:

28 January 2015 (28.01.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/933,246 29 January 2014 (29.01.2014) US
62/078,895 12 November 2014 (12.11.2014) US(71) Applicant: NEUROPORE THERAPIES, INC. [US/US];
10835 Road to the Cure, Suite 210, San Diego, CA 92121 (US).

(72) Inventors: STOCKING, Emily, M.; c/o Neuropore Therapies, Inc., 10835 Road to the Cure, Suite 210, San Diego, CA 92121 (US). WRASIDLO, Wolfgang; c/o Neuropore Therapies, Inc., 10835 Road to the Cure, Suite 210, San Diego, CA 92121 (US).

(74) Agents: MULLEN, James, J., III et al.; Morrison & Foerster LLP, 12531 High Bluff Drive, Suite 100, San Diego, CA 92130-2040 (US).

(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, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

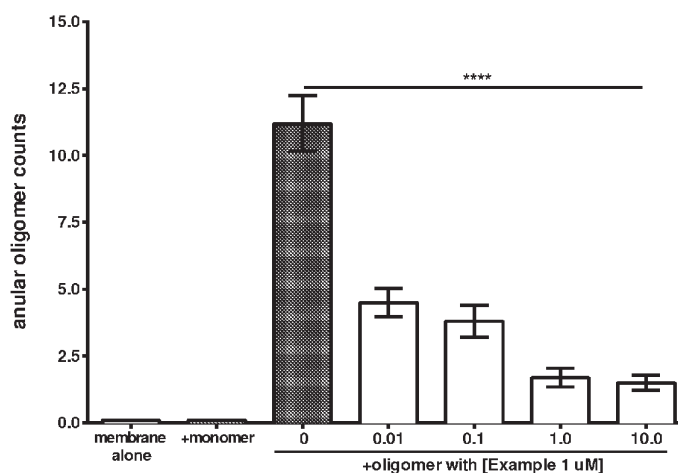
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

(54) Title: HETEROARLY AMIDES AS INHIBITORS OF PROTEIN AGGREGATION

Figure 2



(57) Abstract: The present invention relates to certain heteroaryl amide compounds, pharmaceutical compositions containing them, and methods of using them, including methods for preventing, reversing, slowing, or inhibiting protein aggregation, and methods of treating diseases that are associated with protein aggregation, including neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Lewy body disease, Parkinson's disease with dementia, fronto-temporal dementia, Huntington's Disease, amyotrophic lateral sclerosis, and multiple system atrophy, and cancer and melanoma.

PATENT COOPERATION TREATY

RECEIVED

JAN 19 2016

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

MORRISON & FOERSTER LLP
SAN DIEGO

To:

McElhone Katharine E.
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
San Diego CA 92130-2040
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

07.01.2016

Applicant's or agent's file reference
699462000840

IMPORTANT NOTIFICATION

International application No.
PCT/US2015/013263

International filing date (day/month/year)
28.01.2015

Priority date (day/month/year)
29.01.2014

Applicant
Neuropore Therapies, Inc.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Authorized Officer

Currie, Susan

Tel. +49 89 2399-8031



PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 699462000840	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/US2015/013263	International filing date (<i>day/month/year</i>) 28.01.2015	Priority date (<i>day/month/year</i>) 29.01.2014	
International Patent Classification (IPC) or national classification and IPC INV. C07D417/14			
Applicant Neuropore Therapies, Inc.			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (<i>sent to the applicant and to the International Bureau</i>) a total of <u>12</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand 25.11.2015		Date of completion of this report 07.01.2016	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Authorized officer Wolf, Claudia Telephone No. +49 89 2399-8285	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2015/013263

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-61 as originally filed

Sequence listings, SEQ ID NO

1 as originally filed

Claims, Numbers

1-38 filed with the letter of

24-11-2015

Drawings, Sheets

1/12-12/12 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2015/013263

5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).
6. ☒ With regard to top-up searches (Rules 66.1ter and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 02.12.2015 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-38</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-38</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-38</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

item V

1 Reference is made to the following documents:

D1 WO 2010/142801 A1 (UNIV LEUVEN KATH [BE]; REMYND [BE];
GRIFFIOEN GERARD [BE]; VAN DOOREN) 16 December 2010
(2010-12-16)

D2 WO 2011/084642 A1 (NEUROPORE THERAPIES INC [US]; MASLIAH
ELIEZER [US]; ROCKENSTEIN EDWARD) 14 July 2011 (2011-07-14)
cited in the application

2 In the light of D1 and D2 the subject matter claimed appears to be novel and
involve an inventive step (Articles 33(2) and (3) PCT).

3 The subject matter claimed refers to compounds of general formula (I) (claims
1- and claim 2), a pharmaceutical composition (claim 3) and a method of
treating a disease (claim 4; however, see point 6 below).

4 The subject matter now on file has been restricted so that hydrogen has been
removed from the definition of R². New claims 5-38 have been added based
upon the disclosure as originally filed, no new matter has been added.

5 D1 and D2 disclose compounds useful for treating neurodegenerative
diseases associated with protein aggregation like the presently claimed
compounds.

The compounds of D1 differ structurally from the presently claimed
compounds in that the prior art compounds all disclose hydrogen as a
substituent corresponding to the substituent R² as presently claimed.

D2 discloses in claim 1 compounds of a general formula (I) which encompass
the compounds of general formula (I) as presently claimed in generic form.
None of the examples disclosed in D2 are novelty-destroying to the subject
matter claimed. As regards the broad general formula (I) of D2 and the
narrowly claimed general formula (I) of the present application the subject
matter claimed appears to be a novel selection of the generic disclosure of
D2.

The comparative compounds A and B disclosed on page 51 of the present
application appear to have been taken from D2. The examples of D2 differ
structurally from the presently claimed compounds in R² as presently claimed.

- 6 The technical problem underlying the present application in the light of D2 as closest prior art when assessing the inventive step of the subject matter claimed may be seen in the provision of further compounds useful in treating neurodegenerative diseases.

A person skilled in the art faced with the task of solving said technical problem would have arrived at the claimed compounds without inventive ingenuity since they are already encompassed in D1 and D2 in generic form and known to be effective for the desired purpose. However, the Applicant has provided comparative test results on pages 51ff of the description to demonstrate that the presently claimed compounds exhibit a superior surprising effect over some compounds chosen from D2. The prior art compounds A and B differ structurally from the presently claimed compounds in substituent R² as presently claimed and are thus structurally very closely related to the claimed compounds. In the light of these test results the subject matter claimed appears to involve an inventive step since the solution to the technical problem is non-obvious in the light of the prior art.

- 7 Claims 4, 36, 37 and 38 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the patentability of the subject-matter of these claims (Article 34(4)(a)(I) PCT) in its present formulation but only on the alleged effect of the compounds as claimed. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

I hereby certify that this correspondence is being transmitted via facsimile 011 49
(0)89 2399 4465

Dated: November 24, 2015 Signature: /Janelle Humphrey/
(Janelle Humphrey)

Docket No.: 699462000840

**IN THE EUROPEAN PATENT OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
(IPEA/EP)**

International Application No.	PCT/US2015/013263
International Filing Date	28 January 2015 (28.01.2015)
Earliest Priority Date	29 January 2014 (29.01.2014)
Applicant	NEUROPORE THERAPIES, INC.
Title	HETEROARYL AMIDES AS INHIBITORS OF PROTEIN AGGREGATION

**RESPONSE TO WRITTEN OPINION WITH CHAPTER II DEMAND
AND ARTICLE 34 AMENDMENTS**

Authorized Officer Susan Currie
European Patent Office
Bob-van-Benthen-Platz 1
80469 Munich
Germany

Dear Officer Currie:

This submission is filed in response to a Written Opinion mailed 23 April 2015. The Response is filed before the Article 34 deadline of 29 November 2015.

A Chapter II Demand accompanies this Response.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

sd-668936

Application No.: PCT/US2015/013263

Docket No.: 699462000840

REMARKS

Status of the Claims

Prior to entry of this response, claims 1-4 were pending. With this response, claims 1-4 have been amended, and new claims 5-38 have been added. Support for the amendments appears in the specification as filed at, for example, paragraphs 11, 14-16, 40-50, 78, and 79. No new matter has been added by way of these amendments.

Novelty/Inventive Step (Item V)

According to the Written Opinion, claims 1-4 lack novelty over D1 (WO2010/142801) and lack inventive step over of D1 and D2 (WO2011/084642). Although a final inventive step assessment was reserved for novel subject matter, the Written Opinion acknowledges that the comparative data provided in the application show the claimed compounds "exhibit a superior surprising effect" over compounds from D2 and could support an inventive step finding once the novelty requirement has been satisfied.

Claim 1 has been amended to recite that R^2 is $-CF_3$ or C_{1-4} alkyl unsubstituted or substituted with halo or $-CF_3$. Claim 1, as amended, does not overlap with the general description in D1 nor does it encompass the particular cited structure (D61). Thus, the present claims, including new claims 5-38, are novel over D1. With respect to inventive step, neither D1 nor D2 provides guidance to select compounds and modify them as needed to arrive at the claimed compounds. Further the comparative data provided in the specification does demonstrate inventive step relative to D2 for the novel subject matter set forth in the present claims.

No opinion was provided for claim 4 beyond the subject matter of the compounds themselves. Applicant directs the Examiner to new claims 35-38, which are in formats suitable for review by the Authority.

Item VIII

The Written Opinion notes that claims 3 and 4 refer to compounds of Formula (I) without reference to a specific claim or claims. These claims have been amended herein to refer to any one of the compound claims.

sd-668936

Application No.: PCT/US2015/013263

Docket No.: 699462000840

In light of the amendments and discussion presented herein, Applicant respectfully requests reconsideration of the findings of lack of novelty and inventive step and issuance of a favorable International Preliminary Report on Patentability (IPRP).

Dated: November 25, 2015

Respectfully submitted,

Electronic signature:

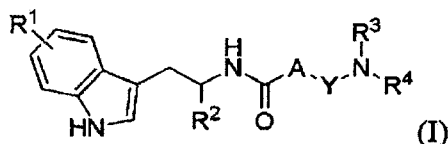
/ Katharine E. McElhone /
Katharine E. McElhone,
Registration No.: 57,462
MORRISON & FOERSTER LLP
12531 High Bluff Drive, Suite 100
San Diego, California 92130-2040
Telephone: (858) 720-7997
Facsimile: (858) 720-5125

Application No.: PCT/US2015/013263

Docket No.: 699462000840

APPENDIX A. CLAIMS (CLEAN VERSION)

1. A compound of Formula (I):



wherein

R¹ is H, halo, C₁₋₄alkyl, or CF₃;

R₂² is -CF₃ or C₁₋₄alkyl unsubstituted or substituted with halo or -CF₃;

A is a 5-membered heteroaryl ring;

Y is absent or is C₁₋₄alkylene;

where Y is absent or is C₁₋₄alkylene, R³ and R⁴ taken together with the nitrogen to which they are attached form a monocyclic heterocycloalkyl ring, unsubstituted or substituted with C₁₋₄alkyl; or

where Y is C₁₋₄alkylene, R³ and Y taken together with the nitrogen to which R³ is attached form a monocyclic heterocycloalkyl ring, and R⁴ is H or C₁₋₄alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound selected from the group consisting of:

	N-(1-(1H-Indol-3-yl)hexan-2-yl)-2-(4-methylpiperazin-1-yl)thiazole-5-carboxamide
	N-(1-(1H-Indol-3-yl)hexan-2-yl)-2-(piperazin-1-yl)thiazole-5-carboxamide
	N-(1-(1H-Indol-3-yl)hexan-2-yl)-2-(2-(4-methylpiperazin-1-yl)ethyl)thiazole-5-carboxamide

sd-668936

13

Application No.: PCT/US2015/013263

Docket No.: 699462000840

	N-(1-(1H-Indol-3-yl)hexan-2-yl)-2-(4-methylpiperazin-1-yl)oxazole-5-carboxamide
	N-(1-(1H-Indol-3-yl)hexan-2-yl)-5-(4-methylpiperazin-1-yl)-1,3,4-thiadiazole-2-carboxamide
	N-(1-(1H-Indol-3-yl)hexan-2-yl)-5-(4-methylpiperazin-1-yl)-4H-1,2,4-triazole-3-carboxamide
	N-(1-(1H-Indol-3-yl)hexan-2-yl)-2-(4-methylpiperazin-1-yl)-1H-imidazole-5-carboxamide
	N-(1-(5-Fluoro-1H-indol-3-yl)hexan-2-yl)-2-(2-morpholinoethyl)thiazole-5-carboxamide
	N-(1-(1H-Indol-3-yl)hexan-2-yl)-2-morpholinothiazole-5-carboxamide
	N-(1-(1H-indol-3-yl)hexan-2-yl)-2-(pyrrolidin-1-yl)thiazole-5-carboxamide

sd-668936

14

Application No.: PCT/US2015/013263

Docket No.: 699462000840

	N-(1-(1H-indol-3-yl)hexan-2-yl)-2-(2-morpholinoethyl)thiazole-5-carboxamide
	N-(1-(5-fluoro-1H-indol-3-yl)hexan-2-yl)-2-(4-methylpiperazin-1-yl)thiazole-5-carboxamide
	N-(1-(6-fluoro-1H-indol-3-yl)hexan-2-yl)-2-(4-methylpiperazin-1-yl)thiazole-5-carboxamide
	N-(1-(5,6-difluoro-1H-indol-3-yl)hexan-2-yl)-2-(4-methylpiperazin-1-yl)thiazole-5-carboxamide
	2-(4-methylpiperazin-1-yl)-N-(6,6,6-trifluoro-1-(1H-indol-3-yl)hexan-2-yl)thiazole-5-carboxamide
	N-(1-(1H-indol-3-yl)hexan-2-yl)-5-morpholino-1,3,4-thiadiazole-2-carboxamide
	N-(1-(1H-indol-3-yl)hexan-2-yl)-5-(2-(4-methylpiperazin-1-yl)ethyl)-1,3,4-thiadiazole-2-carboxamide

sd-668936

15

Application No.: PCT/US2015/013263

Docket No.: 699462000840

	N-(1-(5-fluoro-1H-indol-3-yl)hexan-2-yl)-5-(2-(4-methylpiperazin-1-yl)ethyl)-1,3,4-thiadiazole-2-carboxamide
	N-(1-(1H-indol-3-yl)hexan-2-yl)-2-(1-methylpiperidin-4-yl)thiazole-5-carboxamide
	N-(1-(1H-indol-3-yl)hexan-2-yl)-5-(pyrrolidin-1-yl)-1,3,4-thiadiazole-2-carboxamide
	N-(1-(1H-indol-3-yl)hexan-2-yl)-5-(1-methylpiperidin-4-yl)-1,3,4-thiadiazole-2-carboxamide
	N-(1-(1H-indol-3-yl)hexan-2-yl)-2-(4-methyl-1,4-diazepan-1-yl)thiazole-5-carboxamide
	(S)-N-(1-(1H-Indol-3-yl)hexan-2-yl)-2-(4-methylpiperazin-1-yl)thiazole-5-carboxamide and
	(R)-N-(1-(1H-Indol-3-yl)hexan-2-yl)-2-(4-methylpiperazin-1-yl)thiazole-5-carboxamide

and pharmaceutically acceptable salts thereof.

sd-668936

Application No.: PCT/US2015/013263

Docket No.: 699462000840

3. A pharmaceutical composition comprising (a) at least one compound or pharmaceutically acceptable salt thereof according to any one of claims 1-2 or 5-34, and (b) a pharmaceutically acceptable excipient.
4. A method of treating a disease or medical condition associated with protein aggregation, comprising administering to a subject in need of such treatment an effective amount of at least one compound or pharmaceutically acceptable salt thereof according to any one of claims 1-2 or 5-34.
5. The compound of claim 1, wherein R^1 is H, fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl.
6. The compound of claim 1, wherein R^1 is H or fluoro.
7. The compound of any one of claims 1 or 5-6, wherein R^2 is $-CF_3$, or is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl, each unsubstituted or substituted with fluoro, chloro, bromo, or $-CF_3$.
8. The compound of any one of claims 1 or 5-6, wherein R^2 is $-CF_3$ or is C_{1-4} alkyl optionally substituted with halo or $-CF_3$.
9. The compound of any one of claims 1 or 5-6, wherein R^2 is C_{3-4} alkyl, unsubstituted or substituted with fluoro or $-CF_3$.
10. The compound of any one of claims 1 or 5-6, wherein R^2 is butyl.
11. The compound of any one of claims 1 or 5-6, wherein R^2 is propyl substituted with $-CF_3$.
12. The compound of any one of claims 1 or 5-6, wherein R^2 is in an "R" stereochemical configuration.
13. The compound of any one of claims 1 or 5-6, wherein R^2 is in an "S" stereochemical

sd-668936

Application No.: PCT/US2015/013263

Docket No.: 699462000840

configuration.

14. The compound of any one of claims 1 or 5-6, wherein R^2 is substantially an "R" or substantially an "S" stereochemical configuration.
15. The compound of any one of claims 1 or 5-14, wherein A is a 5-membered heteroaryl ring with two or three heteroatom ring atoms.
16. The compound of any one of claims 1 or 5-14, wherein A is a 5-membered heteroaryl ring with two non-adjacent heteroatom ring atoms.
17. The compound of any one of claims 1 or 5-14, wherein A is thiazole, thiadiazole, oxazole, imidazole, or triazole.
18. The compound of any one of claims 1 or 5-14, wherein A is thiazole or thiadiazole.
19. The compound of any one of claims 1 or 5-14, wherein A is thiazole.
20. The compound of any one of claims 1 or 5-14, wherein Y is absent.
21. The compound of any one of claims 1 or 5-14, wherein Y is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-(\text{CH}_2)_3-$, $-\text{C}(\text{CH}_3)_2-$, $-(\text{CH}_2)_4-$, $-\text{CH}((\text{CH}_2)_2\text{CH}_3)-$, $-\text{CH}(\text{CH}(\text{CH}_3)_2)-$, $-\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)(\text{CH}_2)_2-$, or $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$.
22. The compound of claim 21, wherein Y is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{CH}(\text{CH}_3)-$.
23. The compound of claim 21, wherein Y is $-\text{CH}_2\text{CH}_2-$.
24. The compound of any one of claims 1 or 5-23, wherein R^3 and R^4 are taken together with the nitrogen to which they are attached form a monocyclic heterocycloalkyl ring, unsubstituted or substituted with C_{1-4} alkyl.

sd-668936

Application No.: PCT/US2015/013263

Docket No.: 699462000840

25. The compound of claim 24, wherein R^3 and R^4 taken together with the nitrogen to which they are attached form azetidine, pyrrolidine, piperidine, azepine, piperazine, morpholine, thiomorpholine, or 1,1-dioxo-thiomorpholine, each unsubstituted or substituted with C_{1-4} alkyl.

26. The compound of claim 24, wherein R^3 and R^4 taken together with the nitrogen to which they are attached form piperazine, morpholine, or pyrrolidine, each unsubstituted or substituted with C_{1-4} alkyl.

27. The compound of claim 24, wherein R^3 and R^4 taken together with the nitrogen to which they are attached form piperazine or morpholine, each unsubstituted or substituted with C_{1-4} alkyl.

28. The compound of claim 24, wherein R^3 and R^4 taken together with the nitrogen to which they are attached form piperazine, unsubstituted or substituted with C_{1-4} alkyl.

29. The compound of claim 24, wherein R^3 and R^4 taken together with the nitrogen to which they are attached form piperazine or 4-methyl-piperazine.

30. The compound of any one of claims 1, 5-19, or 21-23, wherein Y is C_{1-4} alkylene, and R^3 and Y taken together with the nitrogen to which R^3 is attached form a monocyclic heterocycloalkyl ring, and R^4 is H or C_{1-4} alkyl.

31. The compound of claim 30, wherein Y and R^3 taken together with the nitrogen to which R^3 is attached form pyrrolidine or piperidine.

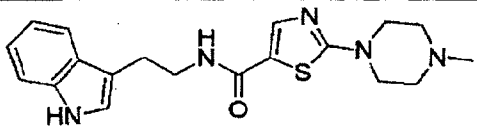
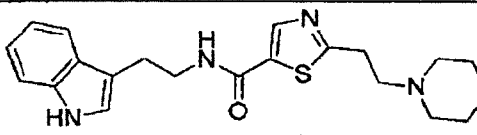
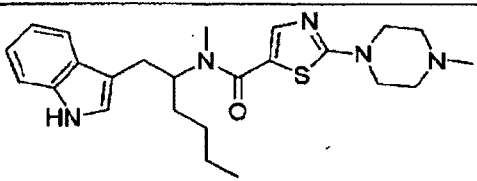
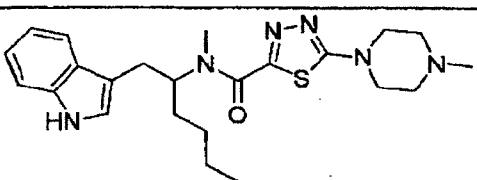
32. The compound of claim 30 or claim 31, wherein R^4 is H or methyl.

33. The compound of claim 1, wherein R^1 is H, R^2 is C_{1-4} alkyl, A is thiazole, Y is absent or is ethylene, and R^3 and R^4 taken together with the nitrogen to which they are attached form N-methylpiperazine.

34. A compound selected from the group consisting of:

Application No.: PCT/US2015/013263

Docket No.: 699462000840

	N-(2-(1H-Indol-3-yl)ethyl)-2-(4-methylpiperazin-1-yl)thiazole-5-carboxamide
	N-(2-(1H-Indol-3-yl)ethyl)-2-(2-(4-methylpiperazin-1-yl)ethyl)thiazole-5-carboxamide
	N-(1-(1H-indol-3-yl)hexan-2-yl)-N-methyl-2-(4-methylpiperazin-1-yl)thiazole-5-carboxamide
	N-(1-(1H-indol-3-yl)hexan-2-yl)-N-methyl-5-(4-methylpiperazin-1-yl)-1,3,4-thiadiazole-2-carboxamide

and pharmaceutically acceptable salts thereof.

35. A compound or pharmaceutically acceptable salt according to any one of claims 1-2 or 5-34 for use in the preparation of a medicament for the treatment of a disease or medical condition associated with protein aggregation.

36. Use of a compound or pharmaceutically acceptable salt thereof according to any one of claims 1-2 or 5-34 for the treatment of a disease or medical condition associated with protein aggregation.

37. The method of claim 4, the compound or pharmaceutically acceptable salt of claim 35, or the use of claim 36, wherein the disease or medical condition associated with protein aggregation is Alzheimer's disease, Parkinson's disease, fronto-temporal dementia, dementia with Lewy bodies (Lewy body disease), Parkinson's disease with dementia, multiple system atrophy, amyotrophic lateral sclerosis, Huntington's disease, cancer, melanoma, or an inflammatory disease.

sd-668936

20

Application No.: PCT/US2015/013263

Docket No.: 699462000840

38. A method of interfering with the accumulation of protein or peptide aggregates in a cell, or preventing, slowing, reversing, or inhibiting protein or peptide aggregation in a cell, comprising contacting the cell with an effective amount of at least one compound or pharmaceutically acceptable salt according to any one of claims 1-2 or 5-34, and/or with the pharmaceutical composition according to claim 3, wherein the contacting is *in vitro*, *ex vivo*, or *in vivo*.

sd-668936

21