(12) STANDARD PATENT (11) Application No. **AU 2018240527 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
CDC-7-inhibitor compounds and use thereof for the treatment of neurological conditions

(51) International Patent Classification(s)
C07D 473/30 (2006.01) ***A61P 25/28*** (2006.01)
A61K 31/52 (2006.01) ***C07D 473/38*** (2006.01)

(21) Application No: **2018240527** (22) Date of Filing: **2018.03.21**

(87) WIPO No: **WO18/172587**

(30) Priority Data

(31) Number	(32) Date	(33) Country
P 201730399	**2017.03.22**	**ES**

(43) Publication Date: **2018.09.27**
(44) Accepted Journal Date: **2022.05.19**

(71) Applicant(s)
Consejo Superior De Investigaciones Científicas (CSIC)

(72) Inventor(s)
Martinez Gil, Ana;Perez, Daniel I.;Gil Ayuso-Gontán, Carmen;Martin-Requero, Angeles;Rojas Prats, Elisa;Martinez-Gonzalez, Loreto;Perez, Concepción

(74) Agent / Attorney
Halfords IP, GPO Box 4212, Sydney, NSW, 2001, AU

(56) Related Art
US 3232937 A
TRATTNIG, S.M. et al., The Journal of Biological Chemistry, vol. 287, no. 30, (2012), pages 25241 - 25254
SKIPPER, H.E. et al., "Structure-Activity Relationships and Cross-Resistance Observed on Evaluation of a Series of Purine Analogs against Experimental Neoplasms", Cancer Research, (1959), vol. 19, no. 4, pages 425 - 437
LEWIS, L.R. et al., "The Preparation and Antitumor Activity of Certain Derivatives of 6-Mercaptopurine", Journal of Medicinal and Pharmaceutical Chemistry, (1962), vol. 5, no. 3, page 607-617
WAGNER, G. et al., "Immunosuppressive antigen conjugate. Part 19. Synthesis of 6-mercaptopurine protein conjugates by means of imido ester coupling", Pharmazie, (1977), vol. 32, no. 12, pages 748 - 750

(12) SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual
Oficina internacional

(43) Fecha de publicación internacional
27 de septiembre de 2018 (27.09.2018)

WIPO | PCT

(10) Número de publicación internacional
WO 2018/172587 A1

(51) Clasificación internacional de patentes:
C07D 473/30 (2006.01) *A61K 31/52* (2006.01)
C07D 473/38 (2006.01) *A61P 25/28* (2006.01)

(21) Número de la solicitud internacional:
PCT/ES2018/070215

(22) Fecha de presentación internacional:
21 de marzo de 2018 (21.03.2018)

(25) Idioma de presentación: español

(26) Idioma de publicación: español

(30) Datos relativos a la prioridad:
P 201730399 22 de marzo de 2017 (22.03.2017) ES

(71) Solicitante: **CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS (CSIC)** [ES/ES]; C/ Serrano, 117, 28006 Madrid (ES).

(72) Inventores: **MARTINEZ GIL, Ana**; CENTRO DE INVESTIGACIONES BIOLOGICAS (CIB), C/ Ramiro de Maeztu, 9, 28040 Madrid (ES). **PEREZ, Daniel I.**; CENTRO DE INVESTIGACIONES BIOLOGICAS (CIB), C/ Ramiro de Maeztu, 9, 28040 Madrid (ES). **GIL AYUSO-GONTÁN, Carmen**; CENTRO DE INVESTIGACIONES BIOLOGICAS (CIB), C/ Ramiro de Maeztu, 9, 28040 Madrid (ES). **MARTIN-REQUERO, Angeles**; CENTRO DE INVESTIGACIONES BIOLOGICAS (CIB), C/ Ramiro de Maeztu, 9, 28040 Madrid (ES). **ROJAS PRATS, Elisa**; CENTRO DE INVESTIGACIONES BIOLOGICAS (CIB), C/ Ramiro de Maeztu, 9, 28040 Madrid (ES). **MARTINEZ-GONZALEZ, Loreto**; CENTRO DE INVESTIGACIONES BIOLOGICAS (CIB), C/ Ramiro de Maeztu, 9, 28040 Madrid (ES). **PEREZ, Concepción**; INSTITUTO DE QUÍMICA MÉDICA (IQM), C/ Juan de La Cierva, 3, 28006 Madrid (ES).

(74) Mandatario: **PONS ARIÑO, Ángel**; Glorieta de Rubén Darío, 4, 28010 Madrid (ES).

(81) Estados designados *(a menos que se indique otra cosa, para toda clase de protección nacional admisible)*: 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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, 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) Estados designados *(a menos que se indique otra cosa, para toda clase de protección regional admisible)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), euroasiática (AM, AZ, BY, KG, KZ, RU, TJ, TM), europea (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).

Publicada:
— *con informe de búsqueda internacional (Art. 21(3))*
— *antes de la expiración del plazo para modificar las reivindicaciones y para ser republicada si se reciben modificaciones (Regla 48.2(h))*

WO 2018/172587 A1

(54) **Title:** CDC-7-INHIBITOR COMPOUNDS AND USE THEREOF FOR THE TREATMENT OF NEUROLOGICAL CONDITIONS

(54) **Título:** COMPUESTOS INHIBIDORES DE CDC-7 Y SU USO PARA EL TRATAMIENTO DE PATOLOGÍAS NEUROLÓGICAS

(57) **Abstract:** The present invention relates to a series of substituted purine derivatives capable of inhibiting Cdc7 kinase activity and, as such, suitable for use in the treatment of neurological diseases such as, inter alia, Alzheimer's disease, amyotrophic lateral sclerosis or frontotemporal dementia, involving hyperphosphorylation of TDP-43 and the subsequent formation of clusters, induced by Cdc7.

(57) **Resumen:** La presente invención se refiere a una serie de derivados de purina sustituidas que son capaces de inhibir la actividad de la quinasa CDC7, por lo que resultan útiles para el tratamiento de enfermedades neurológicas tales como la enfermedad de Alzheimer, la esclerosis lateral amiotrófica o la demencia frontotemporal, entre otras, donde se produce una hiperfosforilación de TDP-43 y posterior formación de aglomerados inducida por la CDC7.

CDC-7-INHIBITOR COMPOUNDS AND USE THEREOF FOR THE TREATMENT OF NEUROLOGICAL CONDITIONS

DESCRIPTION

The present invention refers to a series of substituted purine derivatives that are capable of inhibiting the activity of CDC7 kinase, making them useful for the treatment and/or prevention of neurological diseases such as amyotrophic lateral sclerosis, Alzheimer's disease or frontotemporal dementia, where hyperphosphorylation of TDP-43 and subsequent formation of aggregates induced by CDC7 are produced.

STATE OF THE ART

Hyperactivity of kinases occurs in many types of diseases and particularly in neurodegenerative diseases and cancer. Hyperphosphorylation of the TDP-43 protein induces the formation of aggregates that have been detected in patients with amyotrophic lateral sclerosis or frontotemporal lobular degeneration. It has been detected that CDC7 kinase is responsible for the dual hyperphosphorylation of TDP-43 in serines 409/410 in certain models, so the inhibition of CDC7 would be an interesting strategy to develop drugs for neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) or frontotemporal lobular degeneration (Lianchko, N. F. et al.), *Ann Neurol.* 2013 74(1): 39-52). There are other neurological diseases also mediated by TDP-43, such as chronic traumatic encephalopathy and age-associated cognitive impairment (Iverson GL, et al., *Neurosci Biobehav Rev.*2015 Sep; 56: 276-293; Nag S, et al., *Neurology*. 2017 Feb 14; 88(7): 653-660; Wilson RS, et al., *JAMA Neurol.* 2013 Nov; 70(11): 1418-1424).

Document US2013/0072506A1 describes 6,8-substituted purine derivatives that are useful for a number of therapeutic and cosmetic uses. Among the possible therapeutic uses, mention is made of the treatment of multiple sclerosis or as anti-neurodegenerative drugs.

Document WO2007/124288A1 describes a series of compounds with an indazole structural nucleus that have the ability to inhibit CDC-7 and that are useful for the treatment of a disease in which this kinase is involved, such as cancer.

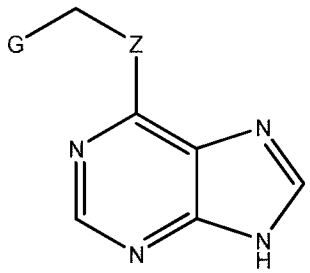
In *ACS Med. Chem. Lett.* 2013, 4, 211-215, Penning et al. describe a study on the interaction of azaindole-derived compounds with the CDC-7 and the possibility of using these compounds in cancer therapy.

Document US2011/015172A1 describes a family of pyrolpyrazines that are kinase-inhibitors such as CDC-7 and their use for the treatment of kinase-associated diseases such as cancer.

DESCRIPTION OF THE INVENTION

The present invention provides a series of purine-derived compounds that are inhibitors of CDC-7 and useful as potential drugs for diseases mediated by TDP-43 proteinopathies, such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia.

Therefore, in one embodiment the present invention seeks to provide the use of a compound formula (I)



(I)

wherein:

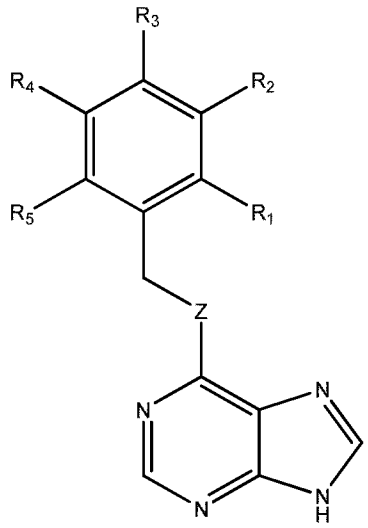
G represents a group selected from aryl, heteroaryl or C_1-C_{10} alkyl, any of which is optionally substituted by at least one substituent selected from CF_3, C_1-C_6 alkyl, S-C_1-C_6 alkyl, halogen, CN, O-C_1-C_6 Alkyl, NO_2, COO-C_1-C_6 Alkyl, NHCO-C_1-C_6 Alkyl, NH_2 and NH-C_1-C_6 alkyl, or optionally substituted by two substituents forming a cycle condensed to group G when it is an aryl or a heteroaryl and

Z is selected from O or S;

2018240527 27 Apr 2022

or any of its pharmaceutically acceptable salts, solvents or isomers for the manufacture of a medicament for the treatment and/or prevention of pathologies related to the TDP-43 protein, in particular with post-translational modifications of TDP-43. These compounds are inhibitors of CDC7 in the phosphorylation of TDP-43.

In a preferred performance G is an aryl group optionally substituted by at least one substituent selected from CF_3, C_1-C_{6b}alkyl, S-C_1-C_6 alkyl, halogen, CN, O-C_1-C_6 alkyl, NO_2, COO-C_1-C_6 alkyl, NHCO-C_1-C_6 alkyl, NH_2 and NH-C_1-C_6 alkyl, or optionally substituted by two substituents forming a cycle condensed to the aryl group, more preferably the aryl group is a phenyl that can optionally be substituted and the compound formula (I) would be the compound formula (II):



(II)

wherein:

R_1 to R_5 are each independently selected from H, CF_3, S-C_1-C_6 Alkyl, halogen, C_1-C_6 Alkyl, CN, O-C_1-C_6 Alkyl, NO_2, COO-C_1-C_6 Alkyl, NHCO-C_1-C_6 alkyl, NH_2 and NH-C_1-C_6 Alkyl or two of the radicals R_1 to R_5 form a phenyl-condensed cycle; and

Z is selected from O or S.

The term "aryl", in the present invention, refers to single or multiple aromatic rings, which have between 5 and 18 carbon atoms in the part of the ring, such as, but not limited to, phenyl, naphthyl, diphenyl, indenyl, phenantryl, fluorenyl or anthracyl Preferably the aryl group has 5 to 7 carbon atoms and more preferably the aryl group is a phenyl. The aryl groups can optionally be substituted in any of their positions by one or more substitutes or by two substitutes forming an aryl condensed cycle and are independently selected

from among such as CF_3, C_1-C_6 alkyl, S-C_1-C_6 alkyl, halogen, CN, O-C_1-C_6 Alkyl, NO_2, COO-C_1-C_6 alkyl, NHCO-C_1-C_6 alkyl, NH_2 and NH-C_1-C_6 alkyl, and more preferably between CF_3, C_1-C_6 alkyl, halogen, CN and NO_2.

The term "heteroaryl" refers to an aryl, as defined above, which contains at least one distinct carbon atom, such as S, N, or O, forming part of the aromatic ring. The heteroaryl groups can optionally be substituted in any of their positions by one or more substituents or by two substituents forming a heteroaryl condensed cycle and are independently selected among such as CF_3, C_1-C_6 alkyl, S-C_1-C_6 alkyl, halogen, CN, O-C_1-C_6 alkyl, NO_2, COO-C_1-C_6 alkyl, NHCO-C_1-C_6 alkyl, NH_2 and NH-C_1-C_6 alkyl, and more preferably between CF_3, C_1-C_6 alkyl, halogen, CN and NO_2.

The term "alkyl" refers, in this invention, to saturated, linear or branched hydrocarbon chains, having from 1 to 10 carbon atoms, e.g. methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *tert*-butyl, *sec*-butyl, n-pentyl, n-hexyl, etc. Preferably the alkyl group has between 1 and 6 carbon atoms and more the alkyl group has between 1 and 3 carbon atoms. Alkyl groups may optionally be replaced by one or more substitutes such as CF_3, C_1-C_6 alkyl, S-C_1-C_6 alkyl, halogen, CN, O-C_1-C_6 alkyl, NO_2, COO-C_1-C_6 alkyl, NHCO-C_1-C_6 alkyl, NH_2 and NH-C_1-C_6alkyl, and more preferably between CF_3, halogen, CN and NO_2.

“Halogen” in this invention means an atom of bromine, chlorine, iodine or fluorine, preferably bromine, chlorine or iodine.

In a preferred realization of the compounds of formula (II), R_1 to R_5 are selected independently of between H, CF_3, halogen, C_1-C_6 alkyl, CN, NO_2 or two of the radicals R_1 to R_5 form a cycle condensed to phenyl.

More preferably R_5 is H and even more preferably at least one of R_1, R_2, R_3 or R_4 is Cl, Br, I, methyl, CF_3, CN or NO_2, more preferably at least one of R_1, R_2, R_3 or R_4 is Cl, Br, I, CF_3, CN or NO_2.

More preferably R_5 is H and even more preferably two of the radicals R_1 to R_4 form a cycle condensed to phenyl, more preferably R_1 and R_2 form a cycle condensed to phenyl, even more preferably forming a naphthyl.

In another preferred performance, R_1, R_2, R_3, R_4 and R_5 are H.

In a more preferred realization the compound formula (I) or (II) is selected from among:

- 6-(benzylthio)-9H-purine (1)
- 6-((Naphthalene-1-ylmethyl)thio)-9H-purine (2)
- 6-((3-(cyanobenzyl)thio)-9H-purine (3)
- 6-((2-(trifluoromethyl)benzyl)thio)-9H-purine (4)
- 6-((4-chlorobenzyl)thio)-9H-purine (5)
- 6-((3-chlorobenzyl)oxy)-9H-purine (6)
- 6-((3-(trifluoromethyl)benzyl)thio)-9H-purine (7)
- 6-((3-chlorobenzyl)thio)-9H-purine (8)
- 6-((3-iodobenzyl)thio)-9H-purine (9)
- 6-((3-nitrobenzyl)thio)-9H-purine (10)
- 6-((3-bromobenzyl)thio)-9H-purine (11)
- 6-((4-bromobenzyl)thio)-9H-purine (12) and
- 6-((2-bromobenzyl)thio)-9H-purine (13)
- 6-((2-chlorobenzyl)thio)-9H-purine (14)
- 6-((3-methoxybenzyl)thio)-9H-purine (15)
- Ethyl 2-((9H-purine-6-yl)thio)methyl)benzoate (16)
- 6-((4-nitrobenzyl)thio)-9H-purine (17)
- 6-((4-acetamidobenzyl)thio)-9H-purine (18)
- 6-((4-cyanobenzyl)thio)-9H-purine (19)
- 6-((benzyl)oxy)-9H-purine (20)
- 6-((4-bromobenzyl)oxy)-9H-purine (21)
- 6-(4-(trifluoromethyl)benzylthio)-9H-purine (22)
- 6-((4-(methylthio)benzyl)thio)-9H-purine (23).

Preferably the TDP-43 related disease is a neurological or neurodegenerative disease and can be selected primarily from amyotrophic lateral sclerosis, frontotemporal dementia and Alzheimer's disease, it can also be selected between chronic traumatic encephalopathy and age-associated cognitive impairment. Preferably the disease is selected between amyotrophic lateral sclerosis, frontotemporal dementia, Alzheimer's disease and age-associated cognitive impairment, even more preferably the disease is amyotrophic lateral sclerosis.

Another aspect of the invention concerns a compound, henceforth composed of the second aspect of the invention, which is selected from among:

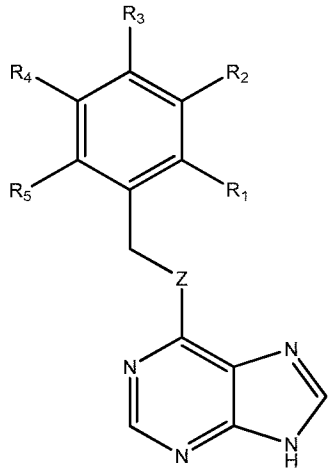
- 6-((Naphthalene-1-ylmethyl)thio)-9H-purine (2)
- 6-((3-(cyanobenzyl)thio)-9H-purine (3)
- 6-((4-chlorobenzyl)thio)-9H-purine (5)
- 6-((3-chlorobenzyl)oxy)-9H-purine (6)
- 6-((3-(trifluoromethyl)benzyl)thio)-9H-purine (7)
- 6-((3-chlorobenzyl)thio)-9H-purine (8)
- 6-((3-iodobenzyl)thio)-9H-purine (9)
- 6-((3-nitrobenzyl)thio)-9H-purine (10) and
- 6-((2-bromobenzyl)thio)-9H-purine (13)
- 6-((2-chlorobenzyl)thio)-9H-purine (14)
- Ethyl 2-((9H-purine-6-yl)thio)methyl)benzoate (16)
- 6-((4-acetamidobenzyl)thio)-9H-purine (18)
- 6-((4-cyanobenzyl)thio)-9H-purine (19)
- 6-((4-bromobenzyl)oxy)-9H-purine (21)
- 6-((4-(methylthio)benzyl)thio)-9H-purine (23).

Another aspect of the present invention relates to a pharmaceutical composition comprising at least one compound of the second aspect of the invention together with a pharmaceutically acceptable vehicle and may optionally comprise another active ingredient.

A further aspect of the present invention refers to the use of a compound of the second aspect of the invention for the manufacture of a medicament.

In a first aspect the present invention provides a use of a compound of formula (II):

2018240527 27 Apr 2022



(II)

wherein R_5 is H and at least one of R_1, R_2, R_3 or R_4 is Cl, Br, I, methyl, CF_3, CN or NO_2; and

Z is selected from O or S;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the treatment and/or prevention of a TDP-43 mediated pathology, wherein the TDP-43 mediated pathology is a neurological disease selected from the group consisting of amyotrophic lateral sclerosis, frontotemporal dementia, Alzheimer's disease, age-associated cognitive impairment, and chronic traumatic encephalopathy.

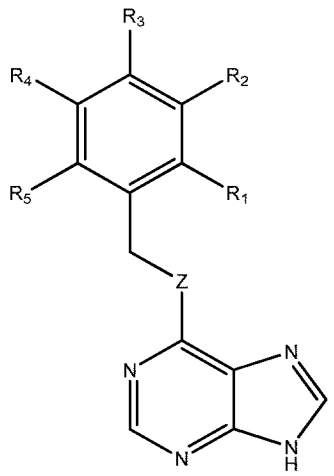
In a second aspect the present invention provides a compound selected from the group consisting of: 6-((3-chlorobenzyl)oxy)-9H-purine, 6-((3-iodobenzyl)thio)-9H-purine, 6-((4-bromobenzyl)oxy)-9H-purine and 6-((4-(methylthio)benzyl)thio)-9H-purine .

In a third aspect the present invention provides a pharmaceutical composition comprising a compound as defined in the second aspect and a pharmaceutically acceptable vehicle.

In a fourth aspect the present invention provides a use of a compound as defined in the second aspect in the manufacture of a medicament.

In a fifth aspect the present invention provides of a method of treating and/or preventing a TDP-43 mediated pathology, wherein the TDP-43 mediated pathology is a neurological disease selected from the group consisting of amyotrophic lateral sclerosis, frontotemporal dementia, Alzheimer's disease, age-associated cognitive impairment,

and chronic traumatic encephalopathy, the method comprising administering to a subject in need thereof an effective amount of a compound of formula (II):



(II)

wherein R_5 is H and at least one of R_1, R_2, R_3 or R_4 is Cl, Br, I, methyl, CF_3, CN or NO_2; and

Z is selected from O or S; or a pharmaceutically acceptable salt thereof.

The compounds of the present invention represented by the formula (I), (II) or by the compounds of the second aspect of the invention, can include isomers, depending on the presence of multiple bonds (for example, Z, E), including optical isomers or enantiomers, depending on the presence of chiral centers. Individual isomers, enantiomers or diastereoisomers and mixtures thereof fall within the scope of the present invention, i.e., the term isomer also refers to any mixture of isomers, such as diastereomers, racemics, etc., including their optically active isomers or mixtures in different proportions thereof. Individual enantiomers or diastereoisomers, as well as their mixtures, can be separated using conventional techniques.

All compounds described in the invention can be in crystalline form as free compounds or as solvates. In this sense, the term "solvate", as used here, includes both pharmaceutically acceptable solvates, i.e., formula (I) compound solvates that may be used in the manufacture of a medicament, and pharmaceutically unacceptable solvates, which may be useful in the preparation of pharmaceutically acceptable solvates or salts. The nature of pharmaceutically acceptable solvent is not critical as long as it is pharmaceutically acceptable. In a particular application, the solvent is a hydrate.

Solvates can be obtained by conventional solvation methods known to experts in the field.

For application in therapy, the compounds of formula (I), (II) or the compounds of the second aspect of the present invention, their salts, solvates or isomers, will be found, preferably, in a pharmaceutically acceptable or substantially pure form, that is to say, that it has a level of pharmaceutically acceptable purity excluding normal pharmaceutical additives such as thinners and carriers, and not including material considered toxic at normal dosage levels. The purity levels for the active ingredient are preferably above 50%, most preferably above 70%, and even more preferably above 90%. In a preferred realization, they are greater than 95% of compound formula (I), (II) or compounds of the second aspect of the present invention, or of its salts, solvates or isomers.

In another respect, the present invention refers to pharmaceutical compositions comprising at least one compound of the invention, or an isomer, a pharmaceutically acceptable salt or a derivative thereof, together with a pharmaceutically acceptable carrier, excipient or vehicle, for administration to a patient.

In a preferred formulation, the pharmaceutical composition also includes another active ingredient.

The pharmaceutically acceptable adjuvants and vehicles that may be used in such compositions are the adjuvants and vehicles known to those skilled in the art and commonly used in the development of therapeutic compositions.

Another aspect of the invention is a method of treatment of a neurological or neurodegenerative disease, which involves the administration to a patient of a therapeutically effective amount of a compound formula (I), preferably formula (II), or of a pharmaceutical composition comprising it, where neurological or neurodegenerative disease is a protein-related disease TDP-43 that can be selected primarily from amyotrophic lateral sclerosis, frontotemporal dementia, Alzheimer's disease, age-associated cognitive impairment, and chronic traumatic encephalopathy.

In the sense used in this description, the term "therapeutically effective quantity" refers to the quantity of the agent or compound capable of developing the therapeutic action

2018240527 27 Apr 2022

determined by its pharmacological properties, calculated to produce the desired effect and, in general, will be determined, among other causes, by the characteristics of the compounds themselves, including age, the state of the patient, the severity of the alteration or disorder, and the route and frequency of administration.

The compounds described in the present invention, their salts or solvates, as well as the pharmaceutical compositions containing them may be used together with other drugs, or additional active ingredients, to provide a combination therapy. Such additional drugs may be part of the same pharmaceutical composition or, alternatively, may be provided in the form of a separate composition for simultaneous or non-simultaneous administration to the pharmaceutical composition comprising a compound of formula (I), preferably a compound of formula (II), or a salt or solvent thereof.

In another particular development, this therapeutic composition is prepared in the form of a solid form or aqueous suspension, in a pharmaceutically acceptable diluent. The therapeutic composition provided by this invention may be administered by any appropriate route of administration, for which such composition shall be formulated in the pharmaceutical form appropriate to the chosen route of administration. In a particular realization, the administration of the therapeutic composition provided by this invention is done orally, topically, rectally or parenterally (including subcutaneous, intraperitoneal, intradermal, intramuscular, intravenous, etc.).

In a preferred realization of the present invention, pharmaceutical compositions are suitable for oral administration, in solid or liquid form. Possible forms for oral administration are tablets, capsules, syrups or solutions and may contain conventional excipients known in the pharmaceutical field, such as aggregating agents (e.g. syrup, acacia, gelatine, sorbitol, tragacanth or polyvinyl pyrrolidone), fillers (e.g. lactose, sugar, corn starch, calcium phosphate, sorbitol or glycine), disintegrants (e.g. starch, polyvinyl pyrrolidone or microcrystalline cellulose) or a pharmaceutically acceptable surfactant such as sodium lauryl sulfate.

The compositions for oral administration can be prepared by the conventional methods of Galenic Pharmacy, as mixture and dispersion. The tablets can be coated following methods known in the pharmaceutical industry.

Pharmaceutical compositions can be adapted for parenteral administration, such as sterile solutions, suspensions, or freeze-dried products of the invention, using the appropriate dose. Suitable excipients, such as pH buffering agents or surfactants, may be used.

The above mentioned formulations can be prepared using conventional methods, such as those described in the Pharmacopoeias of different countries and in other reference texts.

The administration of the compounds or compositions of this invention can be performed by any appropriate method, such as intravenous infusion and oral, intraperitoneal or intravenous routes. Oral administration is preferred for the convenience of patients and for the chronic nature of the diseases to be treated.

The amount of a compound administered from the present invention will depend on the relative efficacy of the compound chosen, the severity of the disease to be treated and the weight of the patient. However, the compounds of this invention will be administered one or more times a day, for example 1, 2, 3 or 4 times a day, with a total dose between 0.1 and 1000 mg/Kg/day. It is important to keep in mind that it may be necessary to introduce variations in the dose, depending on the age and condition of the patient, as well as modifications in the route of administration.

The compounds and compositions of the present invention may be used together with other drugs in combination therapies. Other drugs may be part of the same composition or of a different composition, for administration at the same time or at different times.

The use of the compounds of the invention is compatible with their use in protocols in which the compounds of the formula (I), or their mixtures are used by themselves or in combinations with other treatments or any medical procedure.

Throughout the description and claims the word "comprise" and its variants are not intended to exclude other technical characteristics, additives, components or steps. In other words, where ever it is used, the word “comprise” is to be understood in its “open” sense, that is, in the sense of “including”, and thus not limited to its “closed” sense, that is the sense of “consisting only of”. A corresponding meaning is to be attributed to the

corresponding words “comprising”, “comprised” and “comprises” where they appear. For experts in the field, other objects, advantages and characteristics of the invention will be derived partly from the description and partly from the practice of the invention. The following examples and figures are provided by way of illustration, and are not intended to be limitative of the present invention.

Any reference herein to known prior art does not, unless the contrary indication appears, constitute an admission that such prior art is commonly known by those skilled in the art to which the invention relates, at the priority date of this application.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Shows the linear correlation between the described permeability and the experimental permeability of 10 commercial compounds using the PAMPA methodology.

FIG. 2. Shows the neuroprotective effect of CDC7 inhibitors (compounds 1, 8, 9 and 13) on human SH-SY5Y neuroblastoma cells previously treated with ethacrynic acid (AE, 20 μM) for 12 hours in the presence or absence of inhibitors at 10 μM. The data represent the mean of four different ±SEM experiments (*p <0.05).

FIG. 3. Sample of the effect of CDC7 inhibitors (compounds 1, 8, 9 and 13) on TDP-43 phosphorylation. Quantification and representation of phosphorylated TDP-43 levels by *western blot*.

EXAMPLES

There follow illustrations of the invention by means of assays made by the inventors, which show the effectiveness of the product of the invention.

Example 1: synthesis of the new compounds of the invention.

Compound 1: 6-(benzylthio)-9H-purine

This compound is described in Pathak A.K. et al, *Journal of Medicinal Chemistry*, 2004, 47(1): 273-276.

Compound 2: 6-((Naphthalene-1-ylmethyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. Add 1-(chloromethyl)naphthalene (311.4 mg, 1.76 mmol) and stir overnight at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. The crude compound is purified by chromatographic column using CH_2Cl_2/MeOH (10:1) as eluent. Product 2 is thus obtained in the form of a white solid (218.0 mg, 42 %). ^{1}H-NMR **(500 MHz, DMSO-d_6):** δ 13.55 (s, 1H), 8.81 (s, 1H), 8.42 (s, 1H), 8.19 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.96 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.72 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.63 - 7.52 (m, 2H), 7.45 (dd, *J* = 8.2, 7.0 Hz, 1H), 5.16 (s, 2H). ^{13}C-NMR **(125 MHz, DMSO-d_6):** δ 158.2 (1C), 151.2 (1C), 149.4 (1C), 143.0 (1C), 133.5 (1C), 133.0 (1C), 131.1 (1C), 130.1 (1C), 128.7 (1C), 128.2 (1C), 127.7 (1C), 126.4 (1C), 126.0 (1C), 125.5 (1C), 123.7 (1C), 29.5 (1C), 125.5 (1C), 123.7 (1C), 29.5 (1C), 133.0 (1C), 128.2 (1C), 127.7 (1C), 126.4 (1C), 126.0 (1C), 125.5 (1C), 123.7 (1C), 29.5 (1C). **HPLC:** Purity > 99%, r.t. = 4.33 min. **MS (ES):** m/z 293 [M+1]. **Melting point** 221 – 222 °C. **Elemental analysis ($C_{16}H_{12}N_4S$)** Calculated: C 65.73%, H 4.14%, N 19.16%, S 10.97%. Found: C 65.41%, H 4.07%, N 19.11%, S 10.99%.

Compound 3: 6-((3-(cyanobenzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. Add 3-(bromomethyl)benzonitrile (345.6 mg, 1.76 mmol) and stir overnight at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. It is not necessary to purify by means of a chromatographic column. In this way, product 3 is obtained in the form of a white solid (438.7 mg, 93 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.57 (s, 1H), 8.74 (s, 1H), 8.46 (s, 1H), 7.93 (t, *J* = 1.7 Hz, 1H), 7.85 - 7.79 (m, 1H), 7.71 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 4.70 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 156.9 (1C), 151.4 (1C), 150.2 (1C), 143.5 (1C), 140.1 (1C), 134.0 (1C), 132.4 (1C), 130.9 (1C), 129.7 (2C), 118.6 (1C), 111.3 (1C), 30.7 (1C). **MS (ES):** m/z 268 [M+1]. **Melting point** 189 – 191 °C. **Elemental analysis ($C_{13}H_9N_5S$)** Calculated:

C 58.41%, H 3.39%, N 26.20%, S 12.00%. Found: C 58.46%, H 3.47%, N 26.03%, S 11.84%.

Compound 4: 6-((2-(trifluoromethyl)benzyl)thio)-9H-purine

This compound is described in Kamper C. et al., *Mol Diversity,* 2012, 16(3):541-551.

Compound 5: 6-((4-chlorobenzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. 4-chlorobenzene bromide (362.3 mg, 1.76 mmol) is added and agitated overnight at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. The crude compound is purified by chromatographic column using CH_2Cl_2/MeOH (10:1) as eluent. In this way, the product 5 is obtained in the form of a white solid (387.2 mg, 79 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.55 (s, 1H), 8.73 (s, 1H), 8.45 (s, 1H), 7.55 - 7.43 (m, 2H), 7.42 - 7.29 (m, 2H), 4.65 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 157.8 (1C), 151.4 (1C), 149.4 (1C), 143.2 (1C), 137.2 (1C), 131.7 (1C), 130.8 (2C), 130.0 (1C), 128.4 (2C), 30.8 (1C). **MS (ES):** m/z 279 [M+3], 277 [M+1]. **Melting point** 198 – 200 °C. **Elemental analysis ($C_{12}H_9ClN_4S$)** Calculated: C 52.08%, H 3.28%, N 20.24%, S 11.59%. Found: C 52.19%, H 3.28%, N 20.27%, S 11.59%.

Compound 6: 6-((3-chlorobenzyl)oxy)-9H-purine

Dissolve 3-chlorobenzyl alcohol (2766.2 mg, 19.40 mmol) in NaOH (155.2 mg, 3.88 mmol) and heat until NaOH is dissolved. Cool the solution, add 6-chloro-9H-purine (300.0 mg, 1.94 mmol) and heat to 100 °C for 1 day. Et_2O (120 mL) is added and extracted twice with an aqueous solution of NaOH 1% (70 mL). The aqueous phases are joined, washed with toluene and, after eliminating toluene, neutralised with 37% HCl up to pH 6-8. The solution is cooled in an ice bath and the precipitate obtained is collected by filtration. The crude compound is purified by chromatographic column using CH_2Cl_2/MeOH (10:1) as eluent. In this way, the product 6 is obtained in the form of a white solid (153.7 mg, 30 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.48 (s, 1H), 8.,52 (s, 1H), 8.41 (s, 1H), 7.60 (s, 1H), 7.53 - 7.45 (m, 1H), 7.45 - 7.38 (m, 2H), 5.62 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 158.4 (1C), 155.4 (1C), 151.2 (1C), 143.0 (1C), 139.0 (1C), 133.1 (1C), 130.4 (1C), 128.0 (1C), 127.9 (1C), 126.7 (1C), 118.0 (1C), 66.7 (1C).

Melting point 197 – 199 °C. **Elemental analysis ($C_{12}H_9ClN_4O$)** Calculated: C 55.29%, H 3.48%, N 21.49%. Found: C 55.12%, H 3.51%, N 21.34%.

Compound 7: 6-((3-(trifluoromethyl)benzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. 3-(trifluoromethyl)benzyl bromide (421.4 mg, 1.76 mmol) is added and agitated overnight at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. The crude compound is purified by chromatographic column using CH_2Cl_2/MeOH (10:1) as eluent. This produces product 7 in the form of a white solid (283.3 mg, 52 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.57 (s, 1H), 8.74 (s, 1H), 8.46 (s, 1H), 7.86 (s, 1H), 7.79 (d, *J* = 7.3 Hz, 1H), 7.65 - 7.49 (m, 2H), 4.74 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 157.2 (1C), 151.4 (1C), 150.2 (1C), 143.5 (1C), 139.8 (1C), 133.1 (1C), 129.5 (2C), 129.1 (c, *J* = 31.4 Hz, 1C), 125.5 (c, *J* = 3.9 Hz, 1C), 124.1 (m, 1C), 123.8 (c, *J* = 3.9 Hz, 1C), 30.9 (1C). **MS (ES):** m/z 311 [M+1]. **Melting point** 180 – 182 °C. **Elemental analysis ($C_{13}H_9F_3N_4S$)** Calculated: C 50.32%, H 2.92%, N 18.06%, S 10.33%. Found: C 50.49%, H 3.03%, N 18.03%, S 10.32%.

Compound 8: 6-((3-Chlorobenzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. 3-chlorobenzyl bromide (362.3 mg, 1.76 mmol) is added and agitated overnight at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. The crude compound is purified by chromatographic column using CH_2Cl_2/MeOH (10:1) as eluent. In this way the product 8 is obtained in the form of a white solid (233.1 mg, 48 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.56 (s, 1H), 8.74 (s, 1H), 8.46 (s, 1H), 7.54 (t, *J* = 2.0 Hz, 1H), 7.47 - 7.40 (m, 1H), 7.39 - 7.27 (m, 2H), 4.66 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 157.3 (1C), 151.4 (1C), 149.5 (1C), 143.4 (1C), 140.8 (1C), 132.9 (1C), 130.3 (2C), 128.8 (1C), 127.7 (1C), 127.1 (1C), 30.9 (1C). **MS (ES):** m/z 279 [M+3], 277 [M+1]. **Melting point** 167 – 169 °C. **Elemental analysis**

($C_{12}H_9ClN_4S$) Calculated: C 52.08%, H 3.28%, N 20.24%, S 11.59%. Found: C 51.98%, H 3.28%, N 20.21%, S 11.58%.

Compound 9: 6-((3-Iodobenzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. Add 3-iodobenzyl bromide (523.5 mg, 1.76 mmol) and stir for 4 hours at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. It is not necessary to purify by means of a chromatographic column. In this way, the product 9 is obtained in the form of a pale yellow solid (379.6 mg, 58 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.56 (s, 1H), 8.74 (s, 1H), 8.46 (s, 1H), 7.85 (t, *J* = 1.8 Hz, 1H), 7.60 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.48 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 4.61 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 157.3 (1C), 151.4 (1C), 149.8 (1C), 143.4 (1C), 140.8 (1C), 137.4 (1C), 135.8 (1C), 130.6 (1C), 129.8 (1C), 128.4 (1C), 94.7 (1C), 30.7 (1C). **Melting point** 185 – 187 °C. **Elemental analysis ($C_{12}H_9IN_4S$)** Calculated: C 39.14%, H 2.46%, N 15.22%, S 8.71%. Found: C 39.26%, H 2.53%, N 15.05%, S 8.58%.

Compound 10: 6-((3-nitrobenzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. 3-nitrobenzyl bromide (380.9 mg, 1.76 mmol) is added and agitated for 3 hours at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. It is not necessary to purify by means of a chromatographic column. In this way the product 10 is obtained in the form of a pale yellow solid (460.6 mg, 91 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.58 (s, 1H), 8.74 (s, 1H), 8.47 (s, 1H), 8.36 (t, *J* = 2.0 Hz, 1H), 8.09 (ddd, *J* = 8.4, 2.3, 1.1 Hz, 1H), 7.94 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 4.79 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 156.8 (1C), 151.4 (1C), 150.2 (1C), 147.7 (1C), 143.6 (1C), 140.9 (1C), 135.7 (1C), 129.9 (2C), 123.6 (1C), 122.0 (1C), 30.6 (1C). **Melting point** 193 – 195 °C. **Elemental analysis ($C_{12}H_9N_5O_2S$)** Calculated: C 50.17%, H 3.16%, N 24.38%, S 11.16%. Found: C 50.07%, H 2.76%, N 24.15%, S 11.05%.

Compound 11: 6-((3-bromobenzyl)thio)-9H-purine

This compound is described in Kamper C. et al., *Mol Diversity,* 2012, 16(3):541-551.

Compound 12: 6-((4-bromobenzyl)thio)-9H-purine

This compound is described in Kamper C. et al., *Mol Diversity,* 2012, 16(3):541-551.

Compound 13: 6-((2-bromobenzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol)are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. 2-bromobenzyl bromide (440.6 mg, 1.76 mmol) is added and agitated for 4 hours at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. It is not necessary to purify by means of a chromatographic column. In this way the product 13 is obtained in the form of a white solid (462.3 mg, 82 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.58 (s, 1H), 8.76 (s, 1H), 8.45 (s, 1H), 7.66 (dt, *J* = 7.9, 1.8 Hz, 2H), 7.33 (td, *J* = 7.5, 1.4 Hz, 1H), 7.22 (td, *J* = 7.6, 1.8 Hz, 1H), 4.74 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 157.7 (1C), 151.5 (1C), 149.4 (1C), 143.2 (1C), 136.8 (1C), 132.8 (1C), 131.5 (1C), 130.1 (1C), 129.6 (1C), 128.0 (1C), 124.2 (1C), 32.4 (1C). **Melting point** 209 – 211 °C. **Elemental analysis ($C_{12}H_9BrN_4S$)** Calculated: C 44.87%, H 2.82%, N 17.44%, S 9.98%. Found: C 44.96%, H 2.83%, N 17.43%, S 9.97%.

Compound 14: 6-((2-Chlorobenzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. 2-chlorobenzyl bromide (362.3 mg, 1.76 mmol) is added and agitated overnight at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. The crude compound is purified by chromatographic column using CH_2Cl_2/MeOH (10:1) as eluent. In this way the compound 14 is obtained in the form of a white solid (235.5 mg, 48 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.56 (s, 1H), 8.76 (s, 1H), 8.46 (s, 1H), 7.66 (dd, *J* = 6.4 Hz, 3.0 Hz, 1H), 7.49 (dd, *J* = 6.8, 2.5 Hz, 1H), 7.37 - 7.23 (m, 2H), 4.75 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 157.6 (1C), 151.4 (1C),

149.4 (1C), 143.3 (1C), 135.1 (1C), 133.4 (1C), 131.4 (1C), 130.5 (1C), 129.5 (1C), 129.3 (1C), 127.4 (1C), 29.7 (1C). **MS (ES):** m/z 279 [M+3], 277 [M+1]. **Melting point** 200 – 202 °C. **Elemental analysis ($C_{12}H_9ClN_4S$)** Calculated: C 52.08%, H 3.28%, N 20.24%, S 11.59%. Found: C 52.12%, H 3.33%, N 20.08%, S 11.38%.

Compound 15: 6-((3-methoxybenzyl)thio)-9H-purine

This compound is described in Patthack AK. et al., *J Med Chem,* 2004, 47(1):273-276.

Compound 16: Ethyl 2-(((9H-Purine-6-yl)thio)methyl)benzoate

6-mercaptopurine monohydrate (48.7 mg, 0.29 mmol) and K_2CO_3 (39.5 mg, 0.29 mmol) are dissolved in DMF (4 mL). Keep the reaction mixture in agitation for 1 h at room temperature. Add ethyl 2-(chloromethyl)benzoate (56.8 mg, 0.29 mmol) and stir overnight at room temperature. The solvent is evaporated at reduced pressure and AcOEt (50 mL) is added. The organic phase is washed with distilled water (3 x 50 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. Crude oil is purified by recrystallization in EtOH. In this way the compound 16 is obtained in the form of a white solid (22.0 mg, 24%). ^{1}H-NMR **(500 MHz, DMSO-d_6):** δ 13.51 (s, 1H), 8.73 (s, 1H), 8.41 (s, 1H), 7.87 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.69 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.52 (td, *J* = 7.5, 1.5 Hz, 1H), 7.39 (td, *J* = 7.6, 1.3 Hz, 1H), 4.96 (s, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (125 MHz, DMSO-d_6):** δ 166.6 (1C), 158.3 (1C), 151.3 (1C), 149.3 (1C), 143.0 (1C), 139.4 (1C), 132.3 (1C), 131.4 (1C), 130.4 (1C), 130.0 (1C), 129.5 (1C), 127.6 (1C), 61.0 (1C), 30.0 (1C), 14.0 (1C). **Melting point** 145 – 147 °C. **Elemental analysis ($C_{15}H_{14}N_4O_2S$)** Calculated: C 57.31%, H 4.49%, N 17.82%, S 10.20%. Found: C 56.91%, H 4.72%, N 17.19%, S 9.84%.

Composite 17: 6-((4-nitrobenzyl)thio)-9H-purine

This compound is described in Tromp R. et al., *J Med Chem,* 2004, 47(22):5441-5450.

Compound 18: 6-((4-Acetamidobenzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. Add 4-acetamidobenzyl chloride (323.8 mg, 1.76 mmol) and agitate for 3 h 30 min at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. The crude compound is purified by chromatographic column using

CH_2Cl_2/MeOH (10:1) as eluent. In this way, compound 18 is obtained in the form of a pale yellow solid (207.2 mg, 39 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.53 (s, 1H), 9.93 (s, 1H), 8.73 (s, 1H), 8.44 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 4.59 (s, 2H), 2.01 (s, 3H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 168.2 (1C), 158.4 (1C), 151.4 (1C), 149.3 (1C), 143.0 (1C), 138.4 (1C), 132.1 (1C), 130.1 (1C) 129.4 (2C), 119.0 (2C), 31.4 (1C), 24.0 (1C). **HPLC:** Purity > 99%, r.t. = 5.25 min. **MS (ES):** m/z 300 [M+1]. **Melting point** 223 - 225 °C. **Elemental analysis ($C_{14}H_{13}N_5OS$)** Calculated: C 56.17%, H 4.38%, N 23.40%, S 10.71%. Found: C 55.54%, H 4.51%, N 22.67%, S 10.27%.

Compound 19: 6-((4-Cyanobenzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. Add 4-cyanobenzyl bromide (345.6 mg, 1.76 mmol) and agitate for 2 hours at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. The crude compound is purified by chromatographic column using CH_2Cl_2/MeOH (10:1) as eluent. In this way the compound 19 is obtained in the form of a white solid (358.7 mg, 76 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.57 (s, 1H), 8.73 (s, 1H), 8.46 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 4.72 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 157.2 (1C), 151.4 (1C), 149.9 (1C), 144.3 (1C), 143.5 (1C), 132.4 (2C), 130.0 (2C), 129.6 (1C), 118.8 (1C), 109.8 (1C), 31.1 (1C). **Melting point** 228 – 230 °C. **Elemental analysis ($C_{13}H_9N_5S$)** Calculated: C 58.41%, H 3.39%, N 26.20%, S 11.99%. Found: C 58.30%, H 3.43%, N 26.10%, S 11.87%.

Compound 20: 6-((benzyl)oxy)-9H-purine

This compound is described in Wanner MJ. et al., *J Med Chem,* 2004, 47(27):6875-6883.

Compound 21: 6-((4-Bromobenzyl)oxy)-9H-purine

Dissolve 4-bromobenzyl alcohol (1815.1 mg, 9.70 mmol) and NaOH (155.2 mg, 3.88 mmol) in a little MeOH (25 mL). The reaction mixture is kept in agitation until the NaOH is dissolved. Add 6-chloro-9H-purine (300.0 mg, 1.94 mmol) and heat to (90 °C) for 2 h. The solvent is evaporated at reduced pressure and AcOEt (50 mL) is added. The organic phase is washed with distilled water (3 x 50 mL) adding a little NaCl. It is then dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. The crude compound is

purified by chromatographic column using CH_2Cl_2/MeOH (10:1) as eluent. In this way the compound 21 is obtained in the form of beige solid (107.2 mg, 18 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.48 (s, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 5.59 (s, 2H). **^{13}C-NMR (75 MHz, DMSO-d_6):** δ 158.5 (1C), 155.3 (1C), 151.2 (1C), 143.0 (1C), 136.0 (1C), 131.4 (2C), 130.4 (2C), 121.3 (1C), 118.1 (1C), 66.8 (1C). **Melting point** °C. **Elemental analysis ($C_{12}H_9BrN_4O$)** Calculated: C 47.24%, H 2.97%, N 18.36%. Found: C 47.06%, H 2.98%, N 18.31%.

Compound 22: 6-(4-(trifluoromethyl)benzylthio)-9H-purine

This compound is described in Kamper C. et al., *Mol Diver,* 2012, 16(3):541-551.

Compound 23: 6-((4-(Methylthio)benzyl)thio)-9H-purine

6-mercaptopurine monohydrate (300.0 mg, 1.76 mmol) and K_2CO_3 (243.7 mg, 1.76 mmol) are dissolved in DMF (25 mL). Keep the reaction mixture in agitation for 1 h at room temperature. Add 4-(methylthio)benzyl bromide (382.8 mg, 1.76 mmol) and stir overnight at room temperature. The solvent is evaporated at reduced pressure and AcOEt (100 mL) is added. The organic phase is washed with distilled water (3 x 100 mL) adding a little NaCl. It is dried on anhydrous Mg_2SO_4, filtered and concentrated to dryness. The crude compound is purified by chromatographic column using CH_2Cl_2/MeOH (10:1) as eluent. In this way, compound 24 is obtained in the form of a white solid (158.0 mg, 31 %). **^{1}H-NMR (300 MHz, DMSO-d_6):** δ 13.53 (s, 1H), 8.73 (s, 1H), 8.44 (s, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 4.61 (s, 2H), 2.44 (s, 3H). **^{13}C-NMR (125 MHz, DMSO-d_6):** δ 158.2 (1C), 151.4 (1C), 149.3 (1C), 143.0 (1C), 136.9 (1C), 134.5 (1C), 130.1 (1C), 129.6 (2C), 126.0 (2C), 31.2 (1C), 14.7 (1C). **MS (ES):** m/z 289 [M+1]. **Melting point** 203 – 205 °C. **Elemental analysis ($C_{13}H_{12}N_4S2$)** Calculated: C 54.14%, H 4.19%, N 19.43%, S 22.24%. Found: C 53.96%, H 4.15%, N 19.34%, S 22.19%.

Example 2: CDC7 inhibition measurement (ADP-Glo technology)™)

The method used is a non-radioactive enzyme inhibition assay using human recombinant CDC7. It is based on luminometric quantification of inhibition using the ADP-Glo™ Kinase Kit. In this test the luminescent signal correlates positively with the amount of adenosine diphosphate (ADP) and the activity of the kinase. All compounds were evaluated at a fixed concentration of 10 μM. For compounds with an inhibition

percentage greater than 50%, a dose-response study is carried out to determine their CI_{50} value (concentration of a compound capable of inhibiting CDC7 function by 50%).

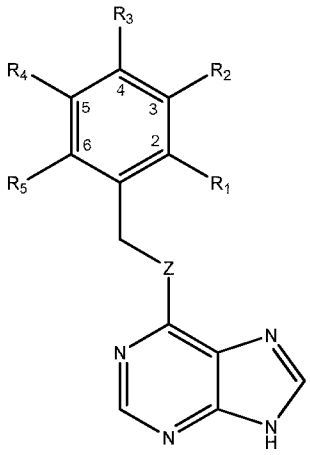
CDC7 enzyme inhibition studies were conducted using the promega kit: ADP-Glo™ *Kinase Assay* + CDC7/DBF4 *Kinase Enzyme System* (Catalogue No. V5089). ATP and other reagents were purchased in Sigma-Aldrich (St. Louis, MO). The trials were performed in a buffer solution using 96-well plates. The compound to be tested (5 µL, 40 µM dissolved in DMSO 4 %) was added to each well followed by the enzyme (5 µL, 25 ng/well), ATP (5 µL, final concentration in well 10 µM) and PDKtidE (5 µL, 4 µg/well). It was then incubated for 60 minutes at room temperature and the reagent ADP-GloTM (20 µL) was added and incubated again for 40 min at room temperature. After incubation, the kinase detection agent (40 µL) was added and incubated for 30 min at room temperature. Finally, the luminescence (integration time of 0.5 - 1 sec) was measured using a POLARstar *Optima multimode reader* polarimeter. Inhibition activities were calculated as a function of maximum activity, measured in the absence of inhibitor. The inhibition values determined for prepared compounds are listed in Table 1.

Example 3: CDC7 inhibition measurement (LanthaScreen technology)

The LanthaScreen Eu kinases inhibition assay uses an Alexa marker Fluor™ that binds to a kinase and is detected by the addition of an Eu-marked antibody. The binding of the marker and the antibody to the kinase results in a high degree of FRET, while the displacement of the marker by an inhibitor results in a loss of FRET. Unlike many other kinase activity tests, this is a simple mix and read test, with no developmental stages. This test method has been developed by Life Technologies and identifies competitive ATP kinase inhibitors, making them suitable for the detection of any compound that binds to the ATP site.

The compounds are evaluated at 1% DMSO (final) in the well. A mixture of human recombinant CDC7/DBF4 (0.5 nM), Eu-antiGST antibody (2 nM) and AlexaFluor marker (1nM) has been used in a buffer of 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 1 mM EGTA in white plates of 348 wells, low volume, coded (Greiner cat. #784207), 160 nL (100 x 100% DMSO compound), 3.84 µL (buffer with CDC7/DBF4), 8.0 µL (antibody), 4.0 µL (marker) are added. Agitate 30 s and incubate at room temperature for 60 min. Then measure the fluorescence in the plate reader and analyze the data (Table 1).

Table 1. Inhibition values in CDC7 of the compounds of formula (II):



(II)

Comp.	R_1 to R_5	Z	CDC7 ADP-Glo™ CI_{50} (μM)	CDC7 Lantha™ CI_{50} (μM)
1	H	S	6.74 ± 0.35	0.125
2	2.3-[$(CH)_4$]	S	11.22 ± 0.84	0,347
3	3-CN	S	8.38 ± 0.27	0.335
4	2-CF_3	S	9.73 ± 1.03	0.245
5	4-Cl	S	8.46 ± 1.05	0.184
6	3-Cl	O	8.98 ± 0.21	0.194
7	3-CF_3	S	6.90 ± 0.83	0.320
8	3-Cl	S	5.21 ± 0.38	0.172
9	3-I	S	3.34 ± 0.27	0.086
10	3-NO_2	S	6.54 ± 0.32	0.189
11	3-Br	S	5.29 ± 0.71	0.138
12	4-Br	S	9.14 ± 0.79	0.438

(continued)

13	2-Br	S	6.24 ± 0.99	0.275
14	2-Cl	S		0.092
15	3-OMe	S		0.239
16	2-CO2Et	S		2.790
17	4-NO2	S		0.127
18	4-NHCOMe	S		0.474
19	4-CN	S		0.288
20	H	O		0.167
21	4-Br	O		0.909
22	4-CF3	S		0.367
23	4-SCH3	S		0.146

Example 3: Prediction of the blood-brain barrier permeation

An essential requirement for drugs for the treatment of neurodegenerative diseases is the ability to cross the blood-brain barrier (BBB), as otherwise they could not act on the target of interest. Therefore, for compounds that are not permeable or located in the area of uncertainty, it may be necessary to properly convey a pharmaceutical formulation through methods known to an expert in the field, such as encapsulation. This capability can be predicted *in vitro* using a method known by the acronym PAMPA *(Parallel Artificial Membrane Permeability Assay*) described by Di et al (Di, L.; Kerns, E. H.; Fan, K.; McConnell, O. J.; Carter, G. T. *Eur. J. Med. Chem.*2003, 38 (3), 223-232) and which has subsequently been fine-tuned in our research group. This method allows predicting the effective permeability through artificial membranes by means of a passive diffusion process.

First of all, it is necessary to validate the method, for which 10 commercial compounds are used whose penetration capacity in the central nervous system (CNS) is known and which are to be specified below, obtaining in this case a good linear correlation between the experimental permeability values *(Pe)* and those described (FIG. 1). This correlation line obtained following the pattern described in the bibliography allows establishing the limits to predict whether or not a compound can cross the blood-brain barrier. Thus, a compound is considered BBB permeable (SNC+) if it has a permeability > 4.48 x 10^{-6} cm-s^{-1}.

For the procedure, between 3-5 mg of caffeine, desipramine, enoxacin, hydrocortisone, ofloxacin, piroxicam and testosterone, 12 mg of promazine and 25 mg of atenolol and verapamil were taken and dissolved in EtOH (1000 µL). 100 µL of these solutions were taken and EtOH (1400 µL) and phosphate buffer (PBS) pH = 7.4 (3500 µL) were added in order to achieve a final EtOH concentration of 30% v/v in solution. Finally, the dissolutions were filtered.

On the other hand, a PBS/EtOH solution (70:30) was added to each well of the acceptance plate (180 µL). The donor plate was impregnated with a porcine brain lipid solution (4 µL) dissolved in dodecane (20 mg mL^{-1}). After 5 min, dissolution of each compound was added to this plate (180 µL).

Of the compounds 1 to 10 evaluated, 1-2 mg were taken and dissolved in EtOH (1500 µL) and phosphate buffer (PBS) pH = 7.4 (3500 µL), filtered and added to the donor plate. With these solutions, the wavelengths at which the compounds absorb are determined and the initial absorbance levels at these wavelengths are measured using a UV absorbance reader. Each sample was analyzed from two to five wavelengths, in three wells and in two independent experiments.

The donor plate was then deposited on the acceptor forming a kind of "sandwich" and incubated for 2 hours and 30 minutes at 25 °C. In this way, the compounds will pass from the donor plate to the acceptor plate through the porcine brain lipid by passive diffusion. After that time, the donor plate is carefully removed and the concentration and final absorbance of both commercial and synthesized compounds is determined. The results obtained are expressed as the mean of the measurements [standard deviation (SD)] of the different experiments carried out and are shown in table 2.

Table 2. Permeability values (*Pe* 10^{-6} cm s^{-1}) in the PAMPA-BHE experiment and prediction of central nervous system (CNS) penetration of formula (II) compounds as also described in Table 1:

Comp.	R_1 to R_5	Z	*Pe* (10^{-6} cm s^{-1})	PAMPA prediction
1	H	S	6.2 ± 1.1	SNC+
2	2.3-[$(CH)_4$]	S	13.2 ± 2.0	SNC+
3	3-CN	S	2.3 ± 0.2	SNC+/-
4	2-CF_3	S	17.5 ± 0.9	SNC+
5	4-Cl	S	12.2 ± 1.2	SNC+
6	3-Cl	O	7.2 ± 0.6	SNC+
7	3-CF_3	S	16.3 ± 0.6	SNC+
8	3-Cl	S	15.1 ± 0.6	SNC+
9	3-I	S	13.8 ± 2.5	SNC+
10	3-NO_2	S	3.9 ± 0.4	SNC+/-
12	4-Br	S	11.5 ± 0.7	SNC+
13	2-Br	S	13.1 ± 0.1	SNC+
14	2-Cl	S	18.1 ± 1.2	SNC+
15	3-OMe	S	5.3 ± 0.8	SNC+
16	2-CO2Et	S	9.7 ± 1.4	SNC+
17	4-NO2	S	5.5 ± 1.3	SNC+
19	4-CN	S	2 ± 0.7	SNC+/-
20	H	O	2.9 ± 0.9	SNC+/-
21	4-Br	O	14 ± 1.4	SNC+

(continued)

22	4-CF3	-	13.5 ± 1.6	SNC+
23	4-SCH3	-	17.8 ± 0.7	SNC+

Example 4: Neuroprotective effect of CDC7 inhibitors against ethacrynic acid

The human neuroblastoma cell line SH-SY5Y was cultured at 37ºC with 5%CO_2 in DMEN medium (Dulbecco´s Modified Eagle Medium) enriched with L-glutamine (2mM), 1% non-essential amino acids, 1% Penicillin/Estreptomycin and 10% fetal bobin serum. In the semiconfluence state, the cells were treated with CDC7 inhibitors (compounds 1 and 8) at different concentrations for 1.30 hours post-addition of the causative agent of TPD-43 phosphorylation; ethacrynic acid (20 µM) (Sigma). After 24 hours, cell viability was evaluated with MTT ([3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) following a described procedure (Denizot F, Lang R. *J Immunol Methods*. 1987; 89:271-7) and levels of western blot phosphorylated TDP-43 (FIG. 2).

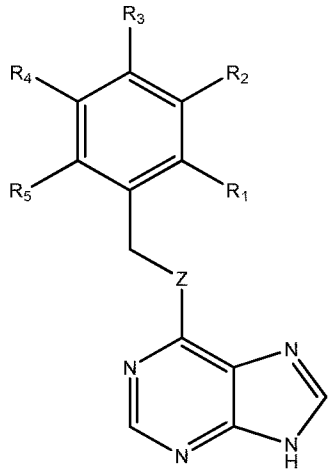
Example 5: Effect of CDC 7 inhibitors on phosphorylation of TDP-43

To evaluate the levels of TDP-43 phosphorylated in the presence of CDC7 inhibitors (compounds 1 and 8), the cells after 24 h of incubation with ethacrylic acid were washed with PBS and then cold lysed with lysis buffer (50mM Tris pH 7.4, 150 mM NaCl, 50 mM NaF, 1% Nonidet P-40 and Protease and phosphatase inhibitors (Roche)). The collected cell extracts were centrifuged for 10 minutes at 4,000 rpm. Protein quantification was performed with the Pierce BCA protein assay kit (Thermo Scientific). 10 µg of protein were loaded into the polyacrylamide gel with SDS and subsequently transferred to a polyvinylidene fluoride (PVDF) membrane (Millipore). The membrane was blocked with 5% bovine serum albumin (Sigma), and incubated for 12 hours with the following primary antibody concentrations (anti-human phosphorus (S409/410)-TDP-43 (1:500) (22309-1AP, Proteintech); α-tubulin (1:1,000) (sc-23948, Santa Cruz Biotechnologies). Amplification of the signal was carried out with secondary antibodies conjugated to radish peroxidase, corresponding to the species used in the primary antibody (Bio-Rad). The density of the bands was quantified with the Image J program (National Institutes of Health, Bethesda, Maryland, USA). FIG. 3 shows that treatment of cells with CDC7 inhibitors (compounds of invention 1 and 8) made it possible to reduce phosphorylation of TDP-43.

2018240527 27 Apr 2022

CLAIMS

1. Use of a compound of formula (II):



(II)

wherein R_5 is H and at least one of R_1, R_2, R_3 or R_4 is Cl, Br, I, methyl, CF_3, CN or NO_2; and

Z is selected from O or S;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the treatment and/or prevention of a TDP-43 mediated pathology, wherein the TDP-43 mediated pathology is a neurological disease selected from the group consisting of amyotrophic lateral sclerosis, frontotemporal dementia, Alzheimer's disease, age-associated cognitive impairment, and chronic traumatic encephalopathy.

2. Use as claimed in claim 1, wherein R_5 is H.

3. Use as claimed in claim 1 or claim 2, wherein at least one of R_1, R_2, R_3 or R_4 is Cl, Br or I.

4. Use as claimed in claim 1 or claim 2, wherein at least one of R_1, R_2, R_3 or R_4 is methyl, CF_3, CN or NO_2.

5. Use as claimed in any one of claims 1 to 4, wherein the compound is selected from the group consisting of:
   - 6-((3-(cyanobenzyl)thio)-9H-purine
   - 6-((2-(trifluoromethyl)benzyl)thio)-9H-purine
   - 6-((4-chlorobenzyl)thio)-9H-purine
   - 6-((3-chlorobenzyl)oxy)-9H-purine
   - 6-((3-(trifluoromethyl)benzyl)thio)-9H-purine
   - 6-((3-chlorobenzyl)thio)-9H-purine
   - 6-((3-iodobenzyl)thio)-9H-purine
   - 6-((3-nitrobenzyl)thio)-9H-purine
   - 6-((3-bromobenzyl)thio)-9H-purine
   - 6-((4-bromobenzyl)thio)-9H-purine
   - 6-((2-bromobenzyl)thio)-9H-purine
   - 6-((2-chlorobenzyl)thio)-9H-purine
   - 6-((4-nitrobenzyl)thio)-9H-purine
   - 6-((4-cyanobenzyl)thio)-9H-purine
   - 6-((4-bromobenzyl)oxy)-9H-purine

   and

   - 6-(4-(trifluoromethyl)benzylthio)-9H-purine.

6. Use as claimed in any one of claims 1 to 5, wherein the neurological disease is selected from amyotrophic lateral sclerosis, frontotemporal dementia and Alzheimer's disease.

7. Compound selected from the group consisting of:
   - 6-((3-chlorobenzyl)oxy)-9H-purine
   - 6-((3-iodobenzyl)thio)-9H-purine
   - 6-((4-bromobenzyl)oxy)-9H-purine

   and

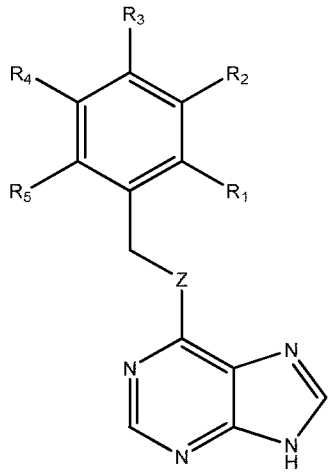
   - 6-((4-(methylthio)benzyl)thio)-9H-purine.

8. Pharmaceutical composition comprising a compound as claimed in claim 7 together with a pharmaceutically acceptable vehicle.

9. Use of a compound as claimed in claim 7 in the manufacture of a medicament.

2018240527 27 Apr 2022

10. A method of treating and/or preventing a TDP-43 mediated pathology, wherein the TDP-43 mediated pathology is a neurological disease selected from the group consisting of amyotrophic lateral sclerosis, frontotemporal dementia, Alzheimer's disease, age-associated cognitive impairment, and chronic traumatic encephalopathy, the method comprising administering to a subject in need thereof an effective amount of a compound of formula (II):



(II)

wherein R_5 is H and at least one of R_1, R_2, R_3 or R_4 is Cl, Br, I, methyl, CF_3, CN or NO_2; and

Z is selected from O or S; or a pharmaceutically acceptable salt thereof.

11. A method as claimed in claim 10, wherein R_5 is H.

12. A method as claimed in claim 10 or claim 11, wherein at least one of R_1, R_2, R_3 or R_4 is Cl, Br or I, or at least one of R_1, R_2, R_3 or R_4 is methyl, CF_3, CN or NO_2.

13. A method as claimed in any one of claims 10 to 12, wherein the compound is selected from the group consisting of:

- 6-((3-(cyanobenzyl)thio)-9H-purine
- 6-((2-(trifluoromethyl)benzyl)thio)-9H-purine
- 6-((4-chlorobenzyl)thio)-9H-purine
- 6-((3-chlorobenzyl)oxy)-9H-purine
- 6-((3-(trifluoromethyl)benzyl)thio)-9H-purine
- 6-((3-chlorobenzyl)thio)-9H-purine

- 6-((3-iodobenzyl)thio)-9H-purine
- 6-((3-nitrobenzyl)thio)-9H-purine
- 6-((3-bromobenzyl)thio)-9H-purine
- 6-((4-bromobenzyl)thio)-9H-purine
- 6-((2-bromobenzyl)thio)-9H-purine
- 6-((2-chlorobenzyl)thio)-9H-purine
- 6-((4-nitrobenzyl)thio)-9H-purine
- 6-((4-cyanobenzyl)thio)-9H-purine
- 6-((4-bromobenzyl)oxy)-9H-purine

and

- 6-(4-(trifluoromethyl)benzylthio)-9H-purine

14. A method as claimed in any one of claims 10 to 13, wherein neurological disease is selected from amyotrophic lateral sclerosis, frontotemporal dementia and Alzheimer's disease.

.

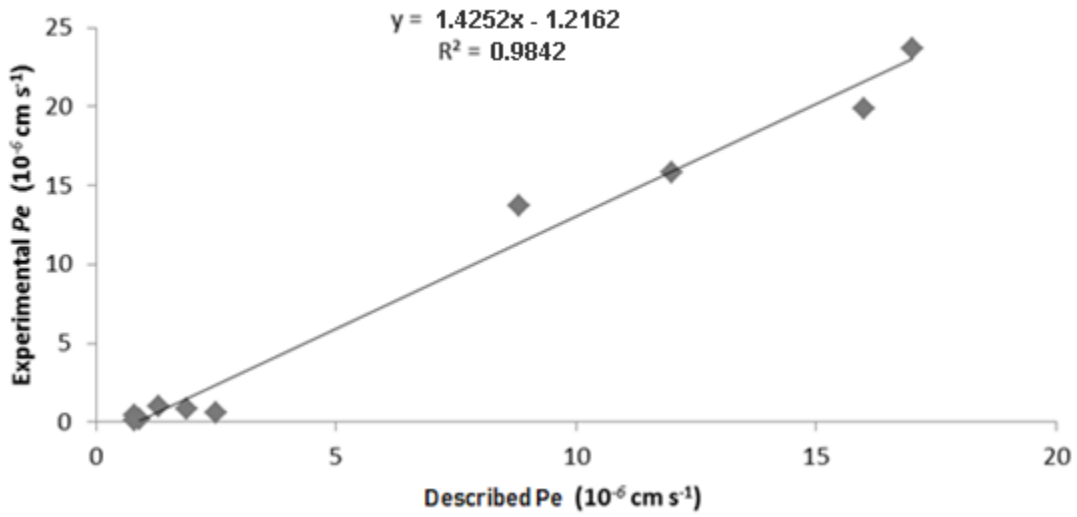

y = 1.4252x - 1.2162
R² = 0.9842
Experimental Pe (10⁻⁶ cm s⁻¹)
Described Pe (10⁻⁶ cm s⁻¹)
0
5
10
15
20
25

FIG. 1

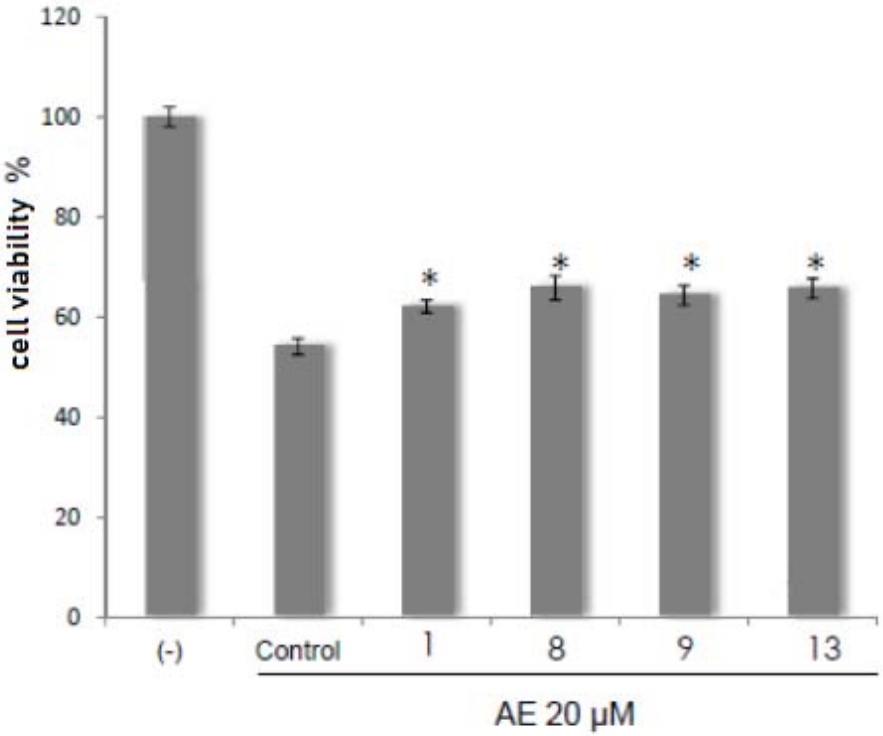

cell viability %
120
100
80
60
40
20
0
(-)
Control
1
8
9
13
AE 20 μM

FIG. 2

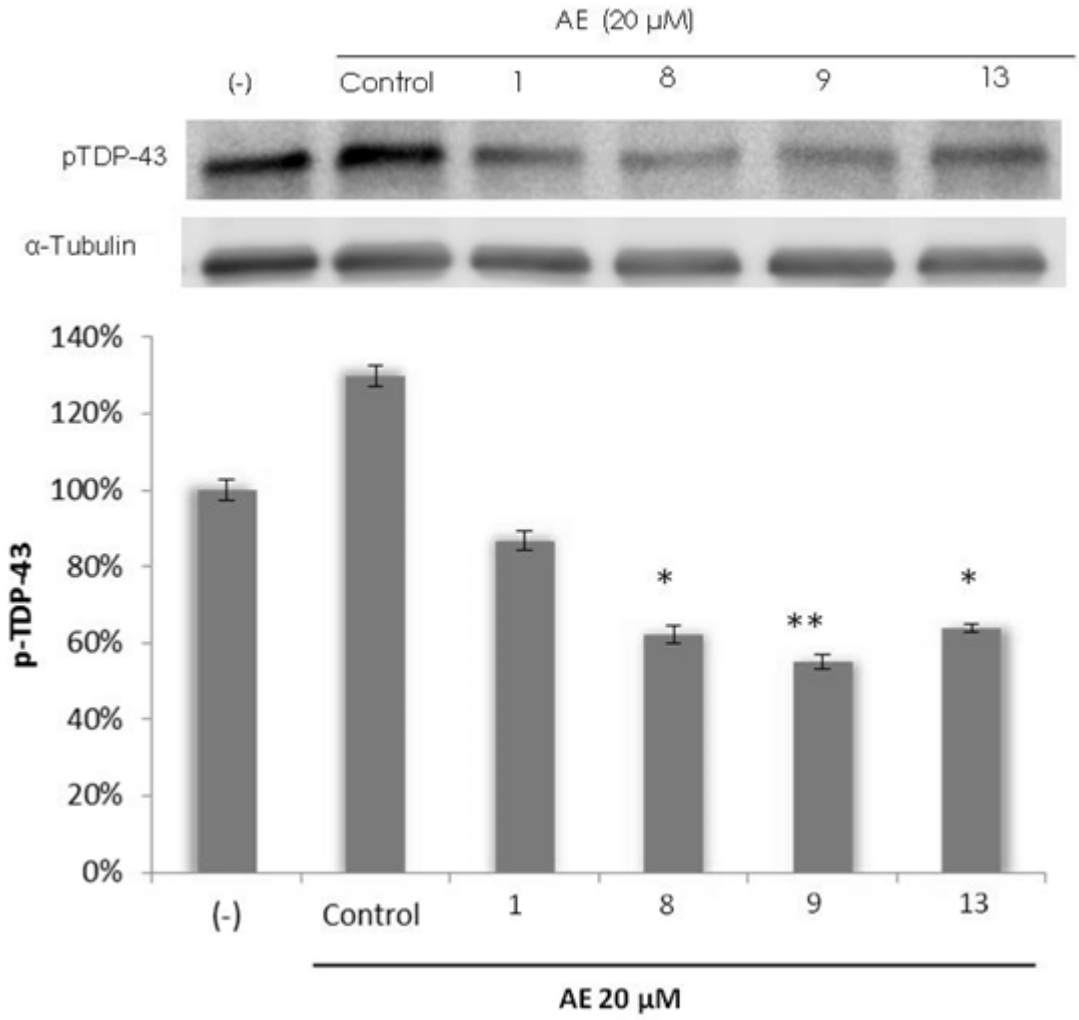

AE (20 μM)
(-)
Control
1
8
9
13
pTDP-43
α-Tubulin
140%
120%
100%
80%
60%
40%
20%
0%
p-TDP-43
*
**
*
(-)
Control
1
8
9
13
AE 20 μM

FIG. 3