



US009775856B2

(12) **United States Patent**
Grases Santos Silva Rauter et al.

(10) **Patent No.:** **US 9,775,856 B2**
 (45) **Date of Patent:** **Oct. 3, 2017**

(54) **C-GLYCOSYLPOLYPHENOL ANTIDIABETIC AGENTS, EFFECT ON GLUCOSE TOLERANCE AND INTERACTION WITH BETA-AMYLOID. THERAPEUTIC APPLICATIONS OF THE SYNTHESIZED AGENT(S) AND OF *GENISTA TENERA* ETHYL ACETATE EXTRACTS CONTAINING SOME OF THOSE AGENTS**

(71) Applicant: **FACULDADE DE CIENCIAS DA UNIVERSIDADE DE LISBOA,**
 Lisbon (PT)

(72) Inventors: **Amélia Pilar Grases Santos Silva Rauter,** Lisbon (PT); **Ana Rita Xavier De Jesus,** Agualva-Cacém (PT); **Alice Isabel Mendes Martins,** Paço De Arcos (PT); **Catarina Alexandra Dos Santos Dias,** Samora Correia (PT); **Rogério José Tavares Ribeiro,** Almada (PT); **Maria Paula Borges De Lemos Macedo,** Lisbon (PT); **Jorge Alberto Guerra Justino,** Santarém (PT); **Helder Dias Mota Filipe,** Sintra (PT); **Rui Manuel Amaro Pinto,** Lisbon (PT); **Bruno Miguel Nogueira Sepodes,** Parede (PT); **Margarida Alexandra Patrício Goulart De Medeiros,** Santarém (PT); **Jesus Jiménez Barbero,** Madrid (ES); **Cristina Airolidi,** Verderio (IT); **Francesco Nicotra,** Milan (IT)

(73) Assignee: **FACULDADE DE CIENCIAS DA UNIVERSIDADE DE LISBOA,**
 Lisbon (PT)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 63 days.

(21) Appl. No.: **14/384,145**

(22) PCT Filed: **Mar. 11, 2013**

(86) PCT No.: **PCT/IB2013/051916**

§ 371 (c)(1),

(2) Date: **Sep. 9, 2014**

(87) PCT Pub. No.: **WO2013/132470**

PCT Pub. Date: **Sep. 12, 2013**

(65) **Prior Publication Data**

US 2015/0031639 A1 Jan. 29, 2015

(30) **Foreign Application Priority Data**

Mar. 9, 2012 (PT) 106202

(51) **Int. Cl.**
A61K 31/7048 (2006.01)
A61K 36/48 (2006.01)

(52) **U.S. Cl.**
 CPC **A61K 31/7048** (2013.01); **A61K 36/48** (2013.01)

(58) **Field of Classification Search**
 None
 See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,482,448 B2 * 11/2002 Tabor A23L 1/2006
 424/757

OTHER PUBLICATIONS

Zhao, L., Chen, Q., & Brinton, R. D. (2002). Neuroprotective and neurotrophic efficacy of phytoestrogens in cultured hippocampal neurons. *Experimental Biology and Medicine*, 227(7), 509-519.*
 Babu, P. V. A., Liu, D., & Gilbert, E. R. (2013). Recent advances in understanding the anti-diabetic actions of dietary flavonoids. *The Journal of nutritional biochemistry*, 24(11), 1777-1789.*
 Rauter, A. P. et al. (2005). Liquid chromatography-diode array detection-electrospray ionisation mass spectrometry/nuclear magnetic resonance analyses of the anti-hyperglycemic flavonoid extract of *Genista tenera* Structure elucidation of a flavonoid/C/ glycoside. *Journal of Chromatography A*, 1089, 59-64.
 Edwards, E. L. et al. (2006). Capillary electrophoresis-mass spectrometry characterisation of secondary metabolites from the antihyperglycaemic plant *Genista tenera*. *Electrophoresis*, 27(11), 2164-2170.
 Reuter, A. P. et al. (2009). Bioactivity studies and chemical profile of the antidiabetic plant *Genista tenera*. *Journal of Ethnopharmacology*, 122(2), 384-393.
 Rauter, A. P. et al. (2010). Antihyperglycaemic and Protective Effects of Flavonoids on Streptozotocin-Induced Diabetic Rats. *Phytotherapy Research*, 24, S133-S138.
 Ikram, Z. M. et al. (2011). Antidiabetic and hypolipidemic effects of the different fractions of methanolic extracts of *Entada phaseoloides* (L.) MERR. in alloxan induced diabetic mice. *International Journal of Pharmaceutical Sciences and Research*, 2(12), 3160-3165.

(Continued)

Primary Examiner — Shaojia Anna Jiang

Assistant Examiner — Dale R Miller

(74) Attorney, Agent, or Firm — Mark M. Friedman

(57) **ABSTRACT**

The present invention concerns the antidiabetic-activity of compounds type A, namely of 8-β-D-glucosylgenistein, which is not toxic to eukaryotic cells and has demonstrated to produce complete normalization of fasting hyperglycaemia, to reduce excessive postprandial glucose excursion, to increase glucose-induced insulin secretion and insulin sensitivity. An alternative synthesis for this molecular entity and its binding ability to β-amyloid oligomers is also included in the present invention, which also comprises *Genista tenera* ethyl acetate extract for use as antihyperglycaemic, agent i.e. for lowering blood glucose levels in mammals that are pre-diabetic or have type 2 or type 1 diabetes. The inhibitory activity of α-glucosidase by *Genista tenera* ethyl acetate and butanol extracts and that of glucose-6-phosphatase by these two extracts and the diethyl ether plant extract is also part of the present invention.

6 Claims, 10 Drawing Sheets