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Grases Santos Silva Rauter et al.

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(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**

(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

(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 Jimenez Barbero**, Madrid (ES); **Cristina Airolidi**, Verderio (IT); **Francesco Nicotra**, Milan (IT)

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

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