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AUGUST 7, 2024

(12) **United States Patent**
Blower et al.

(10) **Patent No.: US 11,370,755 B2**
(45) **Date of Patent: Jun. 28, 2022**

(54) **COMPOSITIONS OF TROFINETIDE**

(71) Applicant: **NEUREN PHARMACEUTICALS LIMITED**, Auckland (NZ)

(72) Inventors: **Clive Blower**, Doncaster East (AU); **Mathew Peterson**, San Diego, CA (US); **James Murray Shaw**, Parkdale (AU); **James Anthony Bonnar**, Ryde (AU); **Etienne David Frank Philippe Moniotte**, Waterloo (BE); **Martin Bernard Catherine Bousmanne**, Woluwe Saint-Lambert (BE); **Cecilia Betti**, Brussels (BE); **Karel Willy Luc Decroos**, Ghent (BE); **Mimoun Ayoub**, Staefa (CH)

(73) Assignee: **NEUREN PHARMACEUTICALS LIMITED**, Auckland (NZ)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/347,135**

(22) Filed: **Jun. 14, 2021**

(65) **Prior Publication Data**

US 2022/0055987 A1 Feb. 24, 2022

Related U.S. Application Data

(63) Continuation of application No. PCT/US2020/044733, filed on Aug. 3, 2020.

(60) Provisional application No. 62/882,998, filed on Aug. 5, 2019.

(51) **Int. Cl.**

C07D 207/16	(2006.01)
B01J 21/06	(2006.01)
B01J 21/18	(2006.01)
B01J 23/44	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 207/16*** (2013.01); ***B01J 21/06*** (2013.01); ***B01J 21/18*** (2013.01); ***B01J 23/44*** (2013.01); *C07B 2200/07* (2013.01)

(58) **Field of Classification Search**

CPC C07D 207/16; B01J 21/06; B01J 21/18; B01J 23/44; C07B 2200/07

USPC 514/359

See application file for complete search history.

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WO WO-2021026066 A1 2/2021

OTHER PUBLICATIONS

Cacciatore, I., et al., "Development of glycine-α-methyl-proline-containing tripeptides with neuroprotective properties," *European Journal of Medicinal Chemistry* 108:553-563, Elsevier, Netherlands (Jan. 2016).

Harris, P., et al., "Synthesis of proline-modified analogues of the neuroprotective agent glycyl-1-prolyl-glutamic acid (GPE)," *Tetrahedron* 61:10018-10035, Elsevier, Netherlands (Oct. 2005).

Pubmed Compound Record for CID 67171960, "(2S)-2-[[(2S)-2-Methyl-1-[2-(phenylmethoxycarbonylamino)acetyl]pyrrolidine-2-carbonyl]amino]pentanedioic acid", U.S. National Library of Medicine, created Nov. 30, 2012, accessed at https://pubchem.ncbi.nlm.nih.gov/compound/67171960, 10 pages.

International Search Report for International Application No. PCT/US2020/044733, USPTO, dated Dec. 7, 2020.

Written Opinion of the International Searching Authority for International Application No. PCT/US2020/044733, USPTO, dated Dec. 7, 2020.

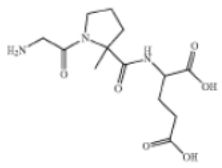
* cited by examiner

Primary Examiner — Taylor V Oh
(74) *Attorney, Agent, or Firm* — Sterne, Kessler, Goldstein & Fox P.L.L.C.

(57) **ABSTRACT**

This disclosure describes compounds of Formula (I), stereoisomers, side compounds thereof, pharmaceutical compositions and methods of manufacturing such compounds, using silylation reagents and producing compositions and products made using such methods. More particularly, this disclosure describes manufacture of trofinetide and side products, compositions and products containing such compounds, for pharmaceutical uses to treat neurodegenerative or neurodevelopmental disorders.

(I)



20 Claims, No Drawings

U.S. Patent 11370755 B2

Initial Patent Review
US 11370755 B2

International Patent Reviews

IPR Initial Review

Patent information

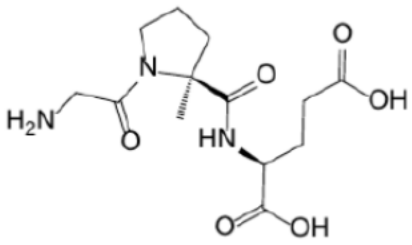
URL	Priority	Expiration	RC*	FC**
https://patents.google.com/patent/US11370755B2/	Aug 8 2019	Aug 3 2040	17	2
https://patents.google.com/patent/US9212204B2/	Jan 27 2011	Jan 27 2032	51	19

*patent and non-patent literature citations ** citing patents

Technology Description & Application Area

Patent Number	Title	Description/Application Area
11370755	Compositions of trofinetide	This disclosure provides for compositions and methods of manufacture containing trofinetide (Glycyl-L-2-Methylprolyl-L-Glutamic acid, or "G-2-MePE"). Compositions are made using new manufacturing methods and contain trofinetide and other products of the synthetic methods.
9212204	Treatment of Rett syndrome using glycyl-L-2-methylprolyl-L-glutamic acid	This invention relates to synthetic analogs and peptidomimetics of glycyl-L-prolyl-L-glutamic acid (GPE). In particular, this invention relates to GPE analogs and peptidomimetics that are anti-apoptotic and anti-necrotic, to methods of making them, to pharmaceutical compositions containing them, and to their use to enhance cognitive function and/or treat memory disorders and to improve neuronal connectivity in animals. More specifically, this application relates to the methods of use of the GPE analog, G-2Methyl-Prolyl-Glutamic acid (G-2-MePE) in the treatment of ASD.

DAYBUE (trofinetide) is designated chemically as (2S)-2-{[(2S)-1-(2-aminoacetyl)-2-methylpyrrolidine-2-carbonyl]amino}pentanedioic acid (IUPAC). Its empirical formula is $C_{13}H_{21}N_3O_6$ and its molecular weight is 315.33 g/mol. The chemical structure is:

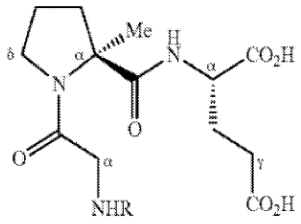


DAYBUE is a pink to red, oral solution with each 5 mL containing 1 g of trofinetide (200 mg/mL). The oral solution also contains FD&C Red No. 40, maltitol, methylparaben sodium, propylparaben sodium, purified water, strawberry flavor, and sucralose as inactive ingredients.

DAYBUE is indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older. (FDA label revision 3/2023)

Prosecution History

11370755	Date	Action/Outcome
Priority	Jun 14 2021	Appl. 17/347,135 is a continuation of Appl. 17/347,135 (filed Aug 3 2020) PCT/US2020/044733 Claims priority from provisional application 62/882,998 (filed Aug 8 2019)
Original Filing	Jun 14 2021	Original filed with Claims 1-71 and amended with Claims 1, 2, 7, 11, 12, 15, 17, 19, 21, 23, 25, 32, 42-44, 47, 72-75
Office Action	Nov 15 2021	Claims 1-2,7, 11-12,15,17, 19, 21, 23, 25, 32, 42-44,47,72-75 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. (In claims 1, 12, 72-75, the term" about " is recited.) Claims 1-2, 7, 11-12,15,17, 19, 21, 23, 25, 32, 42-44,47,72-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making hydrates of the claimed compounds. (In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims. c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. … g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution.)
Office Action	Dec 24 2021	First arguments same as above. Claims 1-2, 11-12, 15 25,42-47 are rejected under 35 U.S.C. 103 as being unpatentable over Glass et al (US2014/0147491 A1) . Glass et al discloses a mixture containing a following compound(see page 13, a pargraph#150) as shown below:

		 G-2MePE: R = H (73:27 trans:cis) 8: R = CH_3 Glass teaches the compound of Formula (II) is absent; provided that at least one of the compounds of Formula (II) or (Ill) is present (see page 14, a pargraph#160). "The filtrate was concentrated to dryness under reduced pressure and the residue triturated with anhydrous diethyl ether to afford a 38:1 mixture of G-2-MePE and tentatively methylamine 8 (0.27 g, 86%) as an extremely hygroscopic white solid",(see page 13, a pargraph#150) . Final Product "G-2-MePE: R=H (73:27 trans:cis)". "8: R=CH3") but does not teach wherein the compound of Formula (Ill) is present in an amount between about 0.001 +-0.0002 wt% and about 2+-0.4 wt%. However, it would have been obvious to one of ordinary skill in the art to be motivated to obtain an amount between about 0.001 +-0.0002 wt% and about 2+ 0.4 wt% of the compound of Formula (111) by routine experimentation by optimizing the reaction conditions, in order to obtain high yield of the compound of Formula (I). … Regarding the Claims 1-2, 11-12, 15 , with respect to the lack of disclosing the amount of a compound of Formula (Ill) between about 0.001 wt% and about 2 wt%, the prior art is silent about it. However, the limitation of a composition claim with respect to the amount in % does not impart patentability to the composition when such a value is one of those which would be determined by one of ordinary skill in the field of art in achieving optimum condition for a particular composition.
Notice of Publication	Feb 24 2022	Published as US 2022/0055987 A1
Response to Office Action	Mar 11 2022	Claim 1 was amended to recite a composition comprising a compound of Formula (I) and a compound of Formula (II). Claims 11, 12, 15, 17, 19, 21, 23,73 and 74 were cancelled. New claims 76-84 added. With regard to 35 U.S.C. § 103: Claims 1, 2, 7, 11, 12, 15, 25, and 42-47 are rejected under 35 U.S.C. § 103 allegedly being unpatentable over US 2014/0147491 ("Glass et al."). According to the Office, Glass et al. discloses a mixture containing instant Formula (I) and instant Formula (III), wherein R J is CH1, and R2, R3, and R4 are hydrogen. See structure on page 9 of Office Action. The Offices alleges that "it would have been obvious to one of ordinary skill in the art to be motivated to obtain an amount between about 0.001 +-0.0002 \Vt%) and about 2+-0.4 wt% of the compound of [Formula (III)] by routine experimentation by optimizing the reaction

		conditions, in order to obtain high yield of the compound of Formula (I)." Office Action, pages 9-10. Applicant traverses this rejection. In order to facilitate prosecution and allowance of this application, and not in acquiescence to the rejection, claim l has been amended to recite in relevant part a composition comprising a compound of Formula (I) and a compound of Formula (II). The Office acknowledges that compositions drawn these two formulae, see claim 72, are not obvious in view of Glass et al. Accordingly, this rejection should be reconsidered and withdrawn.
Notice of Allowance	Apr 1 2022	The rejection of Claims 1-2,7, 11-12,15,17, 19, 21, 23, 25, 32, 42-44,47,72-75 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, is withdrawn due to the modification of the claim 25 and applicant's convincing arguments. The rejection of Claims 1-2, 7, 11-12,15,17, 19, 21, 23, 25, 32, 42-44,47,72-75 are rejected under 35 U.S.C. 112, first paragraph, is withdrawn due to the modification of the claims. The rejection of Claims 1-2, 11-12, 15 25,42-47 under 35 U.S.C. 103 as being unpatentable over Glass et al (US2014/0147491 A1) is withdrawn due to the modification of the claims and applicant's convincing arguments (see page 10, response{quoted above}).
Issue Notification	Jun 8 2022	Notification of issue of US 11370755

9212204	Date	Action/Outcome
Priority	Jan 26 2015	14/605,420 is a Continuation of 13/699,087 (filed 06/05/2013) 13/699,087 is a National Stage Entry of PCT/US2012/000047 (filed 01/27/2012) - -- PCT/US2012/000047 Claims priority from a provisional application 61/492,248 (filed 06/01/2011) PCT/US2012/000047 Claims priority from a provisional application 61/462,141 (filed 01/27/2011)
Original Filing	Jun 14 2021	Original filed with Claims 1-30
Office Action Req. For Restriction/Election	May 11 2015	Restriction to one of the following inventions is required under 35 U.S.C. 121: I. Claims 1-19 and 25-30, drawn to a method of treating an autism spectrum disorder, classified in CPC Subclass A61 K 9/0085. II. Claims 20-24, drawn to a composition, classified in CPC Subclass A61 K 31/401. Species Election For Groups I or II, this application contains claims directed to the following patentably distinct species: Species A: Applicant is required to select a specific autism spectrum disorder (e.g., autism).

		Species B: Applicant is required to select a specific second therapeutic agent by name or chemical formula (e.g., risperidone). Species C: Applicant is required to select a specific sustained release matrix compound by name or chemical formula (e.g., polylactide). Species D: Applicant is required to select a specific route of administration (e.g., oral). The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record where each disorder, agent, compound, and route of administration varies by structure, design, and/or field of search. Applicant is required under 35 U.S.C. 121 to elect a combination of a single Species A, a single Species B, a single Species C, and a single Species D for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, all the claims are generic.
Response to Office Action	May 15 2015	Applicant herein elects Group I Claims 1-19 and 25-30 and withdraws Claims 20-24 without prejudice. The Examiner has issued an Election of Species based on the following species: Specie A: WhichASD? Applicant elects Rett Syndrome Specie B: Second therapeutic agent? Applicant elects respiridone Specie C: Sustained release matrix? Applicant elects polylactide Specie D: Route of administration? Applicant elects oral.
Non-Final Rejection	Jun 23 2015	Claims 1-19 and 25-30 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Sur et al (U.S. Patent Application Pub. No. 2009/0099077 published on 04/16/2009; of record) in view of Gluckman et al (U.S. Patent Application Pub. No. 2007/0298009 published on 12/27/2007). Claims 1-19 and 25-30 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-19 and 29-34 of copending Application No. 13/699,087. (Statutory Double Patenting) Claims 1-19 and 25-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 8,496,963 in view of Sur et al (U.S. Patent Application Pub. No. 2009/0099077 published on 04/16/2009; of record) and Gluckman et al (U.S. Patent Application Pub. No. 2007/0298009 published on 12/27/2007). Claims 1-19 and 25-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,178,125 in view of Sur et al (U.S. Patent Application Pub. No. 2009/0099077 published on 04/16/2009; of record) and Gluckman et al (U.S. Patent Application Pub. No. 2007/0298009 published on 12/27/2007).

Notice of Publication	Jul 16 2015	Title: Treatment of Autism Spectrum Disorders Using Glycyl-L-2-Methylprolyl-L-Glutamic Acid Publication No.US-2015-0197543-A 1 Publication Date:07/16/2015
Notice of Allowance	Apr 1 2022	The rejection of Claims 1-2,7, 11-12,15,17, 19, 21, 23, 25, 32, 42-44,47,72-75 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, is withdrawn due to the modification of the claim 25 and applicant's convincing arguments. The rejection of Claims 1-2, 7, 11-12,15,17, 19, 21, 23, 25, 32, 42-44,47,72-75 are rejected under 35 U.S.C. 112, first paragraph, is withdrawn due to the modification of the claims. The rejection of Claims 1-2, 11-12, 15 25,42-47 under 35 U.S.C. 103 as being unpatentable over Glass et al (US2014/0147491 A1) is withdrawn due to the modification of the claims and applicant's convincing arguments (see page 10, response{quoted above}).
Amendment after Non-Final Rejection	Sep 18 2015	Claims 1, 3, 9, 12, 16, and 17 amended to conform and new claim 31 added. Claims 2, 4-8, 10, 11, 13-15, and 18-30 are cancelled without prejudice. Arguments against double-patenting included: Each and every claim of the '125 patent is directed compositions comprising a "water-in-oil emulsion." Each and every of the claims in the '963 patent is directed to "a water-in-lipid emulsion." Applicant submits that none of the prior issued claims read on an "aqueous solution of G-2-MePE." Applicant submits the only common feature between the instant claims and those of the '125 and '963 patents is the compound, G-2-MePE. Applicant respectfully submits the Declaration of Dr. Clive Blower and the other evidence of objective indicia of non-obviousness to be highly relevant to the instant claims. Arguments against §103 Rejection included: Applicant respectfully submits the rejections to be overcome by evidence presented herein in the form of an Expert Declaration Under 37. C.F.R. 1.132 by Dr. Clive Blower, Ph.D., (the "Blower Declaration")
Notice of Allowance	Oct 7 2015	Allowed
Patent Term Extention	Apr 4 2024	Granted (Undetermined length of extension at present (Jul 7 2024); Applicants submitted a calculated expiration date of Jan 9 2036 [24 years, 11 months, 13 days after filing of first provisional application])

Litigation History

None

Current Orange Book Patent Data

Active Ingredient: TROFINETIDE
Proprietary Name: DAYBUE
Dosage Form; Route of Administration: SOLUTION; ORAL
Strength: 200MG/ML
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N217026
Product Number: 001
Approval Date: Mar 10, 2023
Applicant Holder Full Name: ACADIA PHARMACEUTICALS INC
Marketing Status: Prescription

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	9212204	01/27/2032			U-3556		04/07/2023
001	11370755	08/03/2040	DS	DP			04/07/2023

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
001	NCE	03/10/2028
001	ODE-425	03/10/2030

Some Potential Prior Art

Relevant Patent or Publication	Publication Date
Sara, Vicki R., et al. "Identification of Gly-Pro-Glu (GPE), the aminoterminal tripeptide of insulin-like growth factor 1 which is truncated in brain, as a novel neuroactive peptide." Biochemical and biophysical research communications 165.2 (1989): 766-771.	December 1989
Sara, Vicki R., et al. "The biological role of truncated insulin-like growth factor-1 and the tripeptide GPE in the central nervous system." ANNALS-NEW YORK ACADEMY OF SCIENCES 692 (1993): 183-183.	August 1993
Alexi, Tajrena, et al. "The IGF-I amino-terminal tripeptide glycine-proline-glutamate (GPE) is neuroprotective to striatum in the quinolinic acid lesion animal model of Huntington's disease." Experimental neurology 159.1 (1999): 84-97.	September 1999
Guan, Jian, et al. "N-terminal tripeptide of IGF-1 (GPE) prevents the loss of TH positive neurons after 6-OHDA induced nigral lesion in rats." Brain research 859.2 (2000): 286-292.	March 2000
Aguado-Llera, David, et al. "Gly-Pro-Glu protects β-amyloid-induced somatostatin depletion in the rat cortex." Neuroreport 15.12 (2004): 1979-1982.	August 2004
Cacciatore, Ivana, et al. "GPE and GPE analogues as promising neuroprotective agents." Mini reviews in medicinal chemistry 12.1 (2012): 13-23.	January 2012
Lai, Michelle YH, et al. "Synthesis and pharmacological evaluation of glycine-modified analogues of the neuroprotective agent glycyl-L-prolyl-L-glutamic acid (GPE)." Bioorganic & medicinal chemistry 13.2 (2005): 533-548.	January 2005
Brimble, Margaret A., et al. "Synthesis and pharmacological evaluation of side chain modified glutamic acid analogues of the neuroprotective agent glycyl-L-prolyl-L-glutamic acid (GPE)." Bioorganic & medicinal chemistry 13.2 (2005): 519-532.	January 2005
Trotter, Nicholas S., et al. "Synthesis and neuroprotective activity of analogues of glycyl-l-prolyl-l-glutamic acid (GPE) modified at the α-carboxylic acid." Bioorganic & medicinal chemistry 13.2 (2005): 501-517.	January 2005
**Harris, Paul WR, et al. "Synthesis of proline-modified analogues of the neuroprotective agent glycyl-l-prolyl-glutamic acid (GPE)." Tetrahedron 61.42 (2005): 10018-10035.	October 2005
De Diego, Sergio A. Alonso, et al. "Analogues of the neuroprotective tripeptide Gly-Pro-Glu (GPE): synthesis and structure–activity relationships." Bioorganic & medicinal chemistry letters 15.9 (2005): 2279-2283.	May 2005
De Diego, Sergio A. Alonso, et al. "New Gly-Pro-Glu (GPE) analogues: Expedite solid-phase synthesis and biological activity." Bioorganic & medicinal chemistry letters 16.5 (2006): 1392-1396.	March 2006
Benoiton, N. Leo, et al. "Studies on sensitivity to racemization of activated residues in couplings of N-benzyloxycarbonyldipeptides." International Journal of Peptide and Protein Research 40.6 (1992): 559-566.	December 1992

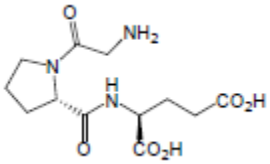
** Only Harris et al., 2005 was cited during prosecution or appears on face of the '755 patent.

Preliminary Analysis

US 11370755 (the '755)

I. Glypromate and its Analogs

The tripeptide Glypromate was first identified in 1989[1]:



GPE quickly became a target of intense research since it was shown to impart neuroprotective effects in the brain[2].

Included in these studies were reports of the synthesis of several neuroprotective GPE analogs including trofinetide[3]. The actual synthesis of trofinetide was known as early as 2005.[4]

More importantly, the synthetic routes by which these compounds, including trofinetide, were made were all very well-established protocols at the time of the invention; many dating back a half century or more.

There is nothing new in the synthesis and production of trofinetide as espoused by the '755.

II. Statutory Requirement

35 U.S.C. 103 (PRE-AIA)

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

III. The Invention

Claim 1 of the '755 is this:

"A composition comprising a compound of [Gly-mePro-Glu] … and between and about 0.001 wt % and about 2 wt% of [Z-Gly-mePro-Glu]."

The purported invention of the '755,therefore, is simply a mixture of a compound and a small amount of a precursor of that compound leftover from the synthetic process used to make it. That is all.

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[1] Sara, Vicki R., et al. "Identification of Gly-Pro-Glu (GPE), the aminoterminal tripeptide of insulin-like growth factor 1 which is truncated in brain, as a novel neuroactive peptide." Biochemical and biophysical research communications 165.2 (1989): 766-771.

[2] Sara et al., 1993; Guan et al., 2000; Alexi et al., 1999; Aguado-Llera, et al., 2004 [see above for full references]

[3] Cacciatore et al., 2012; Lai et al., 2005; Brimble et al., 2005; Trotter et al., 2005; DeDiego et al., 2005; DeDiego et al., 2006 [see above for full references]

[4] Harris et al. "Synthesis of proline-modified analogues of the neuroprotective agent glycyl-l-prolyl-glutamic acid (GPE)." Tetrahedron 61.42 (2005): 10018-10035.

The '755 is not an invention of a new or novel compound, it is not a breakthrough in treatment of a disease by a new (or old) compound, it is not a new method of synthesis. It is simply a claim for a compound plus an impurity found after making that compound.

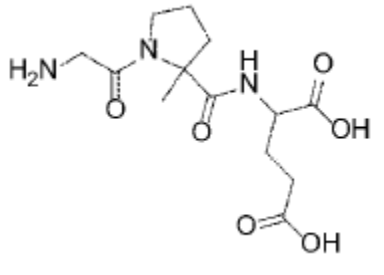
To be more specific, the so-called invention is simply the tripeptide Gly-mePro-Glu (Formula I, below) with some leftover Z-Gly-mePro-Glu (Formula II, below) from the synthetic route employed to make it.

IV. Prosecution of the Invention

Prosecution of the '755 was cursory at best. There was only a single non-final rejection based on Section 103 and citing to US Pub 20140147491 A1 to Glass *et al*. We are of the opinion the rejection should have been upheld.

Claim 1, as examined, was submitted as follows:

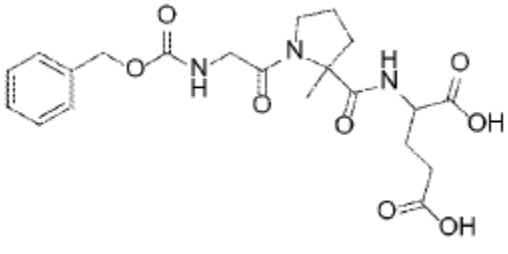
1. (Currently amended) A composition comprising a compound of Formula (I):



(I),

or a stereoisomer, hydrate, or pharmaceutically acceptable salt thereof, and;

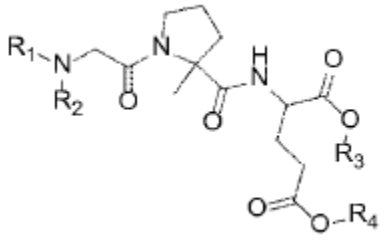
(i) between about 0.001 wt% and about 2 wt% of a compound of Formula (II):



(II),

or a stereoisomer, hydrate, or pharmaceutically acceptable salt thereof [,]] ; or ~~and/or~~

(ii) between about 0.001 wt% and about 2 wt% of a compound of Formula (III):

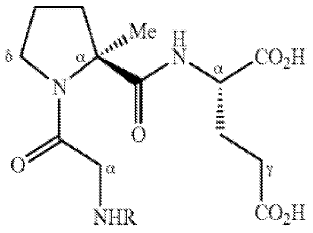


(III),

or a stereoisomer, hydrate, or pharmaceutically acceptable salt thereof, wherein R1, R2, R3 and R4 independently are selected from the group consisting of hydrogen and Ci-4 alkyl, provided at least one ofR1, R2, R3 and R4 is Ci-4 alkyl; or

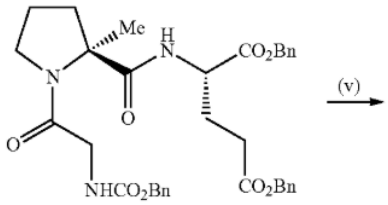
(iii) between about 0.001 wt% and about 2 wt% of a compound of Formula (II), or a stereoisomer, hydrate, or pharmaceutically acceptable salt thereof, and between about 0.001 wt% and about 2 wt% of a compound of Formula (III), or a stereoisomer, hydrate, or pharmaceutically acceptable salt thereof.

Note that Formula (III) is simply a Markush representation of Formula (II). The examiner correctly states that "Glass et al discloses a mixture containing a following compound (see page 13, a pargraph#150) as shown below:"



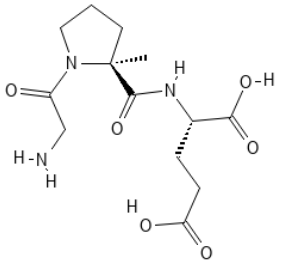
G-2MePE: R = H (73:27 trans:cis)
8: R = CH_3

The examiner, however, goes on to assert that "Glass teaches the compound of Formula (II) is absent; provided that at least one of the compounds of Formula (II) or (Ill) is present." (pg 9 of the Office Action dated Dec. 24, 2020) This is a puzzling statement. Glass made compound (I) via the NαZ, dibenzyl ester. So, we will graphically represent para [0160] of Glass here:

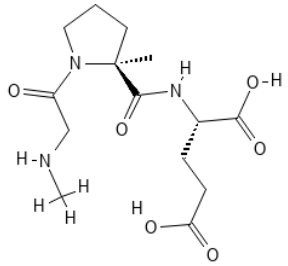


7

where "(v)" is H_2, 10% PdC,91:9 MeOH-H_2O, RT, 23 h (86%).



Gly-mePro-Glu (73:27 cis:trans) +



Sar-mePro-Glu [N-Methylglycyl-2-methyl-L-prolyl-L-glutamic acid]

The examiner then explains that HPLC analysis of the mixture indicated it was a 38:1 mixture of two eluting peaks. Gly-mePro-Glu (*i.e.*, R=H) was shown to be 73:27 trans-cis mixture by ^{1}H-NMR analysis. The other structure identified was Sar-mePro-Glu. In other words, the second peak of Sar-mePro-Glu discloses the Markush structure of Claim 1 (III).

However, it is not apparent that Glass teaches the compound of Formula (II) is *absent*. Glass only teaches that, using HPLC and NMR analysis, two peaks were analyzed.

Moreover, the examiner's contention that "the limitation of a composition claim with respect to the amount in % does not impart patentability to the composition when such a value is one of those which would be determined by one of ordinary skill in the field of art in achieving optimum condition for a particular composition" overlooks the crucial nuances of synthetic pathway and process development. The crux lies not in achieving predetermined impurity thresholds but in actively mitigating impurities to the best of one's abilities. A POSA in the field would aim to optimize the production of the desired compound while minimizing the occurrence of secondary or unreactive processes, which the examiner recognizes but does not apply to Formula II after the deletion of the reference to Formula III.

Inevitably, any process falls short of 100% efficiency, resulting in the formation of byproducts or the persistence of unreacted species. Hence, the focus should not have been on the appearance of Z-Gly-mePro-Glu at any level as a patentable barrier, but rather on recognizing it as an inherent consequence of the described reaction, undesired and non-patentable. In this regard, the examiner's perspective is fundamentally flawed.

As would be expected, in their response to the 103 rejection, the patentee merely deletes the language relating to the Markush group and relies on the examiner's perplexing analysis relative to Formula III. *This minor deletion garnered enough support from the examiner to issue a Notice of Allowance on this shoddy patent.*

The analysis should have turned on whether or not Z-Gly-mePro-Glu was present (inherently) during the synthetic process and, of course, whether, by using the process, Formula II was well known as an impurity. It should not have hinged on whether or not Glass chose to show the presence of all impurities during the synthesis of Formula I or not. (Not only does para[0150] disclose Gly-mePro-Glu, but also shows a scheme for its synthesis.)

If it was a well-known fact that the impurity was always found when using this or other known synthetic pathways, the rejection based on Section 103 (or perhaps even Section 102) should have been upheld. We think it was a well-known fact well-known to a person of ordinary skill in the art of peptide chemistry and synthesis.

V. Artificial extension of Patent Coverage

Glass *et al* claimed priority to a provisional application (61/492,248) filed on June 1, 2011. (It will be noted that the second Orange Book patent, US 9212204, is also a child of this application.) The '755 claims priority to provisional application 62/882998 filed August 5 2019. The estimated expiration date of the '755 is August 3, 2040.

The chemistry used in the '775 was very well known and widely utilized years before the discovery of trofinetide itself. Benzyloxycarbonyl-based protection for peptide synthesis was first described in 1932[5] and very well understood in the industry[6]. Trofinetide itself was ostensibly discovered around mid-2005[7]. If this patent is allowed to stand, it essentially grants protection to a compound for 15 more years that was first discovered at least 20 years ago.

[5] Bergmann, Max, and Leonidas Zervas. "Über ein allgemeines Verfahren der Peptid-synthese." *Berichte der deutschen chemischen Gesellschaft* (A and B Series) 65.7 (1932): 1192-1201

[6] *See, e.g.,* Benoiton, N.L. (2006). Chemistry of Peptide Synthesis (1st ed.). CRC Press, Taylor & Francis Group, Boca Raton, FL

[7] Harris et al., "Synthesis of proline-modified analogues of the neuroprotective agent glycyl-L-prolyl-glutamic acid (GPE)" *Tetrahedron* 2005; 61: 10018–10035

VI. Price of Treatment

The price for treatment for Rett syndrome is estimated to have an annual list price ranging from $575,000 to $595,000 according to Market Watch[8]. Allowing generic competition for this patented composition would result in significant saving for families in need of treatment, hospitals and caregivers.

VII. A word on US 9212204 (the '204 Patent)

We think the '204 is vulnerable as a separate entity. In its response to an initial rejection of its application for the '204, Neuren submitted an affidavit by one of the inventors to ostensibly show evidence of nonobviousness. Without going into great detail here since we are developing these arguments for further action, the assertions made in the affadavit may be problematic for the validity of the '204 in light of a recent Federal Circuit holding from April 2024 discussing method of treatment claims in JANSSEN PHARMACEUTICALS, INC. v. TEVA PHARMACEUTICALS USA, INC.[9] The Court held, in part, that the use of unknown results to argue surprising results is germaine to what a person of ordinary skill in the art would use for motivational information in coming up with the same or similar results.[10] The Court said that

> [t]he [lower] district court concluded that the results were unexpected in view of the '548 protocol too. Although the '548 protocol is the closest prior art, the court did not use the required reference point for evaluating unexpectedness. The question was whether, as of the priority date, using the claimed dosing regimens yielded unexpected results when compared with a POSA's expectations based on the state of the prior art. The court instead based its finding of unexpectedness on two different comparisons: (1) a comparison between Janssen's expectations of the '548 protocol results and its unknown results of the PSY-3003 clinical trial and the results of Invega Sustenna. … Regardless of whether the clinical trial was later considered unsuccessful—and whether this was tied to the dosing regimens used instead of how the trial was conducted—the results of the clinical trial were not known or in the prior art. A POSA could not have been surprised by results of the claimed regimens compared with the '548 protocol results because a POSA would not have been aware of those results. *See Forest Labs.,* 918 F.3d at 937

[8] "Acadia's rare-disease drug to cost $575,000 to $595,000", March 13, 2023. https://www.marketwatch.com/story/acadias-rare-disease-drug-to-cost-575-000-to-595-000-5e883843?mod=search_headline

[9] *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, No. 2022-1258 (Fed. Cir. (D.N.J.) Apr. 1, 2024).

[10] See Id., pg 10, second full paragraph and pages 31-34.