



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : C07K 7/34, 7/10, A61K 37/02 A61K 37/28</p>	<p>A1</p>	<p>(11) International Publication Number: WO 91/11457 (43) International Publication Date: 8 August 1991 (08.08.91)</p>
<p>(21) International Application Number: PCT/US91/00500 (22) International Filing Date: 24 January 1991 (24.01.91) (30) Priority data: 468,736 24 January 1990 (24.01.90) US (60) Parent Application or Grant (63) Related by Continuation US 468,736 (CIP) Filed on 24 January 1990 (24.01.90) (71)(72) Applicants and Inventors: BUCKLEY, Douglas, I. [US/ US]; 215 Brookwood Road, Woodside, CA 94062 (US). HABENER, Joel, F. [US/US]; 217 Plymouth Road, Newton Highlands, MA 02161 (US). MALLORY, Joanne, B. [US/US]; 243 Acalanes, Apt. 9, Sunnyvale, CA 94086 (US). MOJSOV, Svetlana [YU/YU]; 504 East 63rd Street, New York, NY 10021 (US).</p>	<p>(74) Agents: MURASHIGE, Kate, H. et al.; Irell & Manella, 545 Middlefield Road, Suite 200, Menlo Park, CA 94025 (US). (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European pa- tent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (Euro- pean patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i></p>	
<p>(54) Title: GLP-1 ANALOGS USEFUL FOR DIABETES TREATMENT</p> <p>(57) Abstract</p> <p>The invention provides effective analogs of the active GLP-1 peptides, 7-34, 7-35, 7-36, and 7-37, which have improved characteristics for treatment of diabetes Type II. These analogs have amino acid substitutions at positions 7-10 and/or are truncated at the C-terminus and/or contain various other amino acid substitutions in the basic peptide. The analogs may either have an enhanced capacity to stimulate insulin production as compared to glucagon or may exhibit enhanced stability in plasma as compared to GLP-1 (7-37) or both. Either of these properties will enhance the potency of the analog as a therapeutic. Analogs having D-amino acid substitutions in the 7 and 8 positions and/or N-alkylated or N-acylated amino acids in the 7 position are particularly resistant to degradation <i>in vivo</i>.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

5 GLP-1 ANALOGS USEFUL FOR DIABETES TREATMENT

 This is a continuation-in-part of U.S.
Application Serial No. 468,736, filed 24 January 1990.

10 Technical Field

 The invention relates to the field of improved
pharmaceutical compositions. Specifically, the invention
concerns analogs of the glucagon-like peptide I fragment
7-36 or 7-37 with improved pharmacological properties.

15

Background Art

 Glucose metabolism is regulated by a number of
peptide hormones, including insulin, glucagon, and
gastric inhibitory peptide (GIP). The complex mechanism
20 by which these peptide hormones regulate this metabolism
and the manner in which they affect each other is at
least partially elucidated. For example, glucagon binds
to receptors on the surface of the pancreatic beta cells
which produce insulin, and stimulates insulin secretion.
25 Glucagon-like peptide I has been suggested to stimulate
insulin secretion but this has not been confirmed.

 Several of these hormones originate from a mam-
malian glucagon precursor "proglucagon" which is a 180
amino acid peptide. Proteolysis and processing of this
30 peptide results in a number of these protein hormones;
the results of the processing depend on the origin of the
cells in which this occurs. For example, in the pig and
rat pancreas, proglucagon is processed to form glucagon
and glicentin-related pancreatic peptide, a large peptide
35

-2-

which contains both GLP-1 and GLP-2 sequences. In porcine small intestine, the secreted products are the 69 amino acid glucagon-containing peptide glicentin and the two glucagon-like sequences, GLP-1 and GLP-2 as separate peptides.

In any event, however, the overall sequence of proglucagon contains the 29 amino acid sequence of glucagon, the 36 or 37 amino acid sequence of GLP-1 and the 34 amino acid sequence of GLP-2, separated by amino acid spacer sequences.

Early attempts to assign a pattern of activity to GLP-1 gave ambiguous results, and it was subsequently concluded that truncated forms of this peptide are biologically active. Mojsov, S., et al. J Clin Invest (1987) 79:616-619 disclose that only the 31 amino acid peptide GLP-1 (7-37) strongly stimulates the release of insulin from pancreas; although both the truncated and full length 37 amino acid form had earlier been found in pancreas and intestine. It has been demonstrated that GLP-1 (7-36), possibly with the carboxy terminus amidated, is also a potent mediator of insulin release. (See, e.g., Holst, J.J., et al. FEBS Letters (1987) 211:169-174).

The invention described below concerns analogs of these truncated forms of GLP-1, which have desirable combinations of characteristics as they relate to potency in potentiating glucose-induced insulin secretion and glucose-induced inhibition of glucagon secretion and to circulating half-life. The physiological effects of the truncated forms in potentiating glucose-induced insulin secretion have been shown as described above by Holst, J.J., et al. and Mojsov, S., et al. (supra). The activity of the truncated hormones in inhibiting glucagon release has been shown by Orskov, C., et al. Endocrinol

35

(1988) 123:2009-2013; Suzuki, S., et al. Diabetes Research: Clinical Practice (1988) 5(Supp. 1):S30. The circulating half-life of these truncated forms is short--approximately four minutes as shown by Kreyman et al. The Lancet (December 5, 1987) 1300-1303. The modified forms of these truncated GLP-1 peptides provide the opportunity to optimize these properties.

There is some literature relating to the study of degradation of peptide hormones in the liver and in plasma and the half-life of such hormones in vivo generally. An early paper by McDonald, J.K. et al., J Biol Chem (1969) 244:6199-6208 showed that a dipeptidase was responsible for the degradation of glucagon in rat liver. Studies on the growth hormone releasing factor, a member of the general glucagon, GLP-1, GLP-2 family, was shown to be rapidly degraded in plasma in vitro and also in vivo by a dipeptidase, (Frohman, L.A. et al., J Clin Invest (1986) 78:906-913). Murphy, W.A. et al., in Peptide Research (1988) 1:36-41, showed that some but not all alkylated growth hormone releasing factor peptides had higher potency in vivo. In particular, for example, the triisopropylated GRF-29 was found to be 106 times more active than GRF-29 itself. On the other hand, GRF-29 which was in methylated at the N-terminus was only 40% as potent as the parent. It was also shown that substitution of D-Ala position 2 of this hormone enhanced its potency. It was, of course, not certain to what effect on properties the enhancement of potency could be attributed.

Others have attempted some modifications of GLP-1 (7-37). It has been shown that deletion of the histidine residue at position 7 greatly diminishes the activity of the hormone (Suzuki, S., et al. (supra); Hendrick, G.K.; et al. Abstract: Endocrine Society

35

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.