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(54) **GLP-1 EXENDIN-4 PEPTIDE ANALOGS AND USES THEREOF**

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(57) **ABSTRACT**

The invention relates to novel polypeptide analogues of GLP-1 and exendin-4. The polypeptide, in a preferred embodiment, is insulinotropic and long-acting. Preferably, the polypeptide's insulinotropic effect is comparable to or exceeds the effect of an equimolar amount of GLP-1 or exendin-4. The invention also relates to a method of treating a subject with diabetes, comprising administering to the subject the polypeptide of the invention in an amount that has an insulinotropic effect. The invention also relates to methods of using GLP-1, exendin-4, and polypeptide analogues thereof for neuroprotective and neurotrophic effects.

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See application file for complete search history.

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Figure 1
Amino acid sequence of GLP-1 (7-36) (SEQ ID NO:1), exendin-4 (SEQ ID NO:2), and novel peptide analogues

Peptide Name	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48							
AA Charge	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
GLP-1 (SEQ ID NO:1)	H	A	E	G	T	F	T	S	D	W	S	S	S	S	E	G	D	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
EX-4 (SEQ ID NO:2)	H	G	E	G	T	F	T	S	D	W	S	S	S	S	E	G	M	E	E	A	V	R	F	I	E	W	L	K	N	G	C	P	S	S	G	A	P	P	P	S									
AA Charge	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
1 (GLP-1 GLY-9) (SEQ ID NO:3)	H	G	E	G	T	F	T	S	D	W	S	S	S	S	E	G	D	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
Enantiomer	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D		
2 (SEQ ID NO:4)	H	A	E	G	T	F	T	S	D	W	S	S	S	S	E	G	R	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
Enantiomer	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D			
3 (SEQ ID NO:4)	H	A	E	G	T	F	T	S	D	W	S	S	S	S	E	G	D	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
Enantiomer	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D			
5 (SEQ ID NO:4)	H	A	E	G	T	F	T	S	D	W	S	S	S	S	E	G	D	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
Enantiomer	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D			
6 (SEQ ID NO:4)	H	A	E	G	T	F	T	S	D	W	S	S	S	S	E	G	D	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
Enantiomer	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D				
7 (SEQ ID NO:4)	H	A	E	G	T	F	T	S	D	W	S	S	S	S	E	G	R	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
Enantiomer	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D				
8 (SEQ ID NO:5)	H	G	E	G	T	F	T	S	D	W	S	S	S	S	E	G	D	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
Enantiomer	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D				
9 (SEQ ID NO:6)	H	G	E	G	T	F	T	S	D	W	S	S	S	S	E	G	D	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
10 (EX-4 WOT) (SEQ ID NO:7)	H	G	E	G	T	F	T	S	D	W	S	S	S	S	E	G	D	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
Enantiomer	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D				
11 (GLP-1, Ala-6) (SEQ ID NO:8)	H	V	A	E	G	T	F	T	S	D	W	S	S	S	E	G	D	A	V	K	E	F	I	A	W	L	V	M	G	I	R																		
Enantiomer	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D				

Figure 1 (cont.)

12 (SEQ ID NO: 9)	H	A	E	G	T	F	T	S	D	V	S	V	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	K	G	G	R	I	R	S	I	S	G	A	P	R	P	S	
13 (SEQ ID NO: 10)	H	A	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	E	T	P	S	I	S	G	A	P	R	P	S		
14 (SEQ ID NO: 11)	H	A	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
15 (SEQ ID NO: 12)	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
16 (SEQ ID NO: 13)	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
17 (SEQ ID NO: 14)	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
18 (SEQ ID NO: 15)	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
19 (SEQ ID NO: 16)	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
20 (SEQ ID NO: 17)	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
21 (SEQ ID NO: 18)	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
22 (SEQ ID NO: 19)	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
23 (SEQ ID NO: 20)	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
24 (SEQ ID NO: 21)	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	E	F	I	E	W	L	K	N	G	G													
25 (SEQ ID NO: 22)	H	A	E	G	T	F	T	S	D	V	S	V	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	K	G	R													
26 (SEQ ID NO: 23)	H	A	E	G	T	F	T	S	D	V	S	V	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	K	G	R													
27 (SEQ ID NO: 24)	H	G	E	G	T	F	T	S	D	V	S	S	V	M	E	E	A	V	R	E	F	I	A	W	L	V	K	G	R													
28 (SEQ ID NO: 25)	H	G	E	G	T	F	T	S	D	V	S	S	V	M	E	E	A	V	R	E	F	I	A	W	L	V	K	G	R													
29 (SEQ ID NO: 26)	H	G	E	G	T	F	T	S	D	V	S	S	V	M	E	E	A	V	R	E	F	I	A	W	L	V	K	G	R													
30 (SEQ ID NO: 27)	H	G	E	G	T	F	T	S	D	V	S	S	V	M	E	E	A	V	R	E	F	I	A	W	L	V	K	G	R													
31 (SEQ ID NO: 28)	H	G	E	G	T	F	T	S	D	V	S	S	V	M	E	E	A	V	R	E	F	I	A	W	L	V	K	G	R													
32 (SEQ ID NO: 29)	H	G	E	G	T	F	T	S	D	V	S	S	V	M	E	E	A	V	R	E	F	I	A	W	L	V	K	G	R													
33 (SEQ ID NO: 30)	H	G	E	G	T	F	T	S	D	V	S	S	V	M	E	E	A	V	R	E	F	I	A	W	L	V	K	G	R													

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8 A A spacer at 8 and 9

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