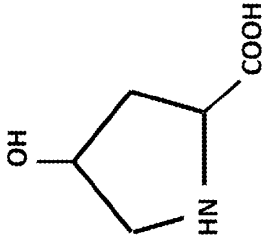


DACRA: Dual Amylin Calcitonin Receptor Agonist

Amylin	KCNTA-TCATQ-RL A EF-LRHSS-NNFG A -ILSST-NVGSN- T Y -NH ₂
Pramlintide	KCNTA-TCATQ-RLA E EF-LRHSS-NNFG P -IL P PT-NVGSN- T Y -NH ₂
Cagrilintide	O-KCNTA-TCATQ-RL A EF-LRHSS-NNFG P -IL P PT-NVGSN- T P -NH ₂
MBX 5129	O- X CNTA-TCATQ-RL A EF-LRHSS-NNFG A -IL Z ST-NVGSN- T Z -NH ₂



Z = L, 4-Hyp (Trans) O = (γE-COC18H32CO2H) X = Beta-lysine

Fig. 1

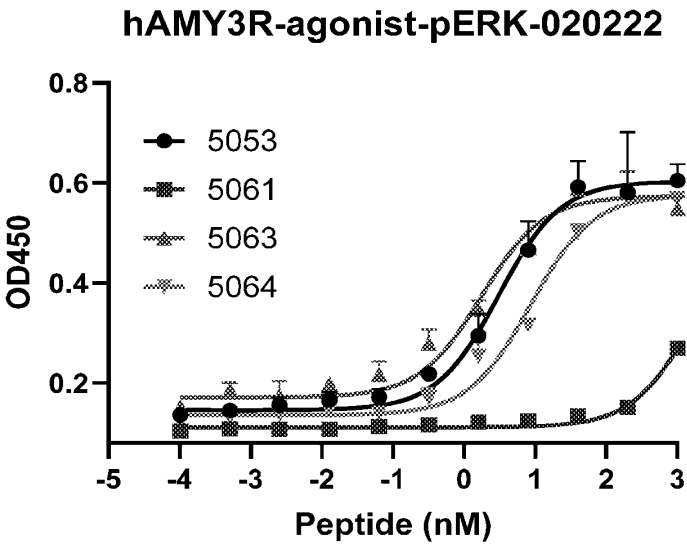


Fig. 2A

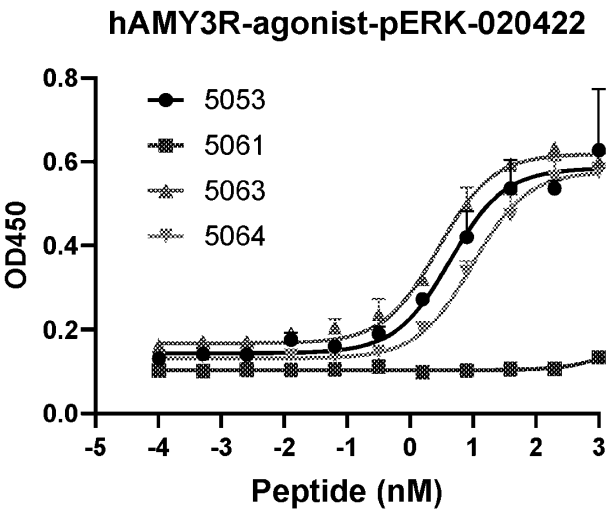


Fig. 2B

5053	O-KCNTA-TCATQ-RLA EF -L R HSS-NNFGP-ILPPT-NVGSN-T P -NH2	
5061	KCNTA-TCATQ-RLANF-LVHSS-NNFG A -ILP ST -NVGSN-TY-NH2	hAmylin Pro28
5063	KCNTA-TCATQ-RLANF-LV R SS-NN L GP-VLPPT-NVGSN-TY-NH2	rAmylin
5064	KCNTA-TCATQ-RLANF-LVHSS-NNFG A -IL X ST-NVGSN-TY-NH2	hAmylin Hyp28

Fig. 2C

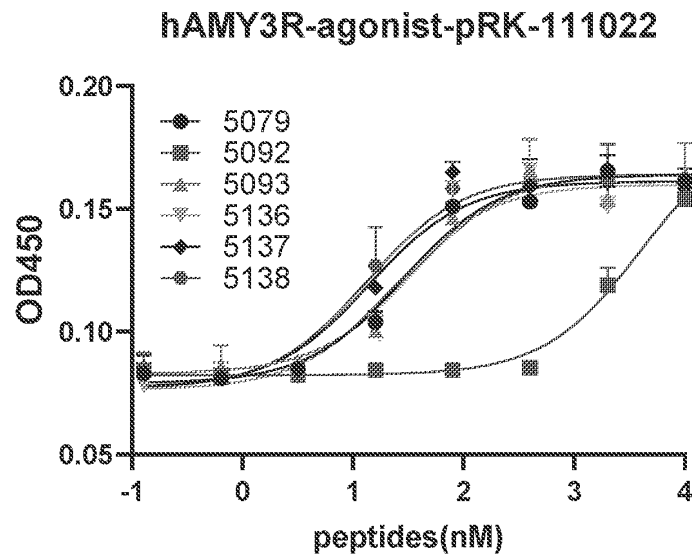


Fig. 3A

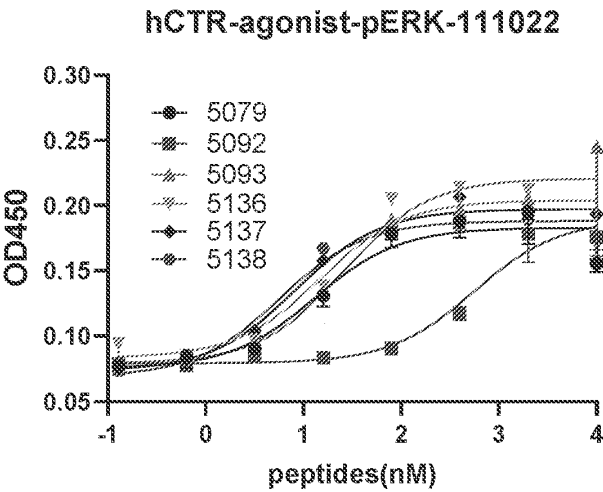


Fig. 3B

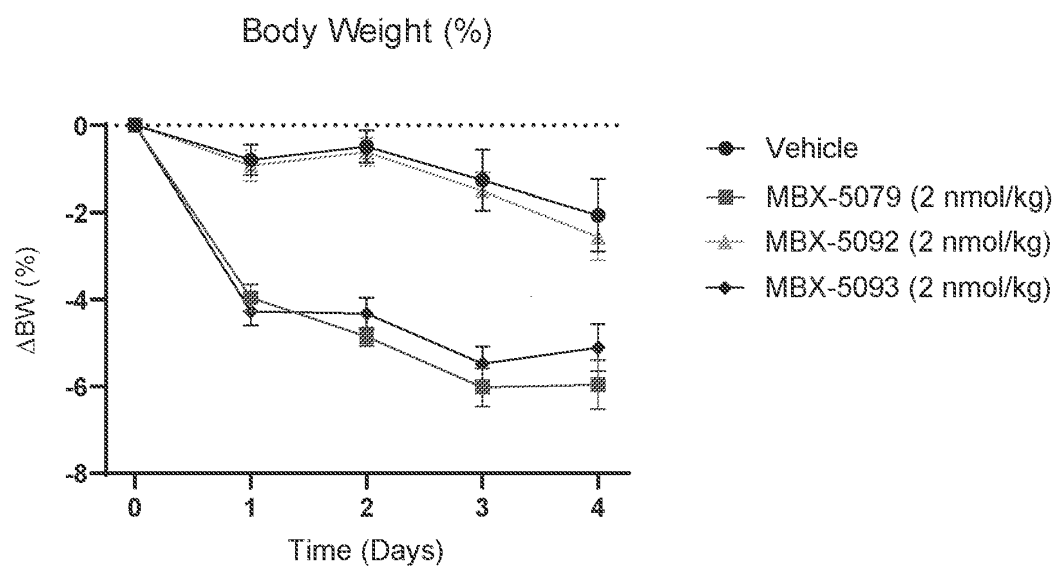
		5079	5092	5093	5136	5137	5138
EC50	hAMY3R	28.46	3909	34.70	23.39	14.07	13.33
EC50	hCTR	13.10	561.5	26.00	14.82	8.308	5.674
5079	O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILXST-NVGSN-TP-NH2						
5092	O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGX-ILSST-NVGSN-TP-NH2						
5093	O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILSXT-NVGSN-TP-NH2						
5136	O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILXXT-NVGSN-TP-NH2						
5137	O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGP-ILXXT-NVGSN-TP-NH2						
5138	O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGX-ILXXT-NVGSN-TP-NH2						

O = (γE-COC18H32CO2H)

X = L,4-Hyp(Trans)

Fig. 3C

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5079 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**X**ST-NVGSN-TP-NH₂

5092 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNFG**X**-ILSST-NVGSN-TP-NH₂

5093 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILS**X**T-NVGSN-TP-NH₂

O = (γE-COC18H32CO₂H)
X = L,4-Hyp(Trans)

Fig. 4

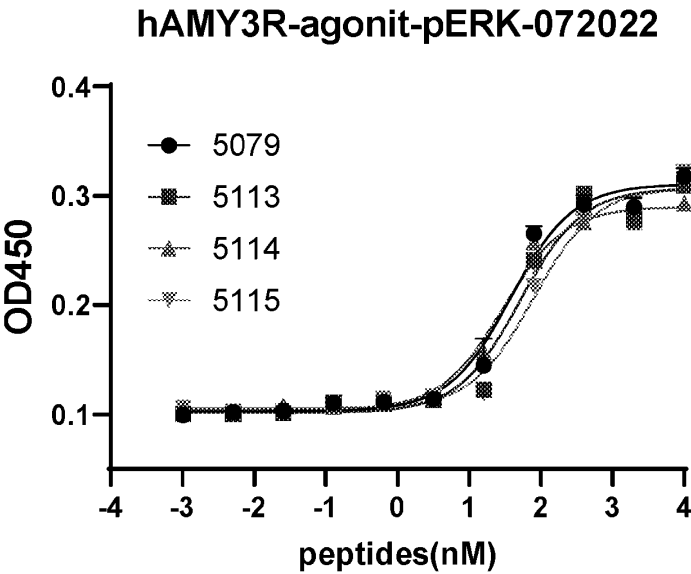


Fig. 5A

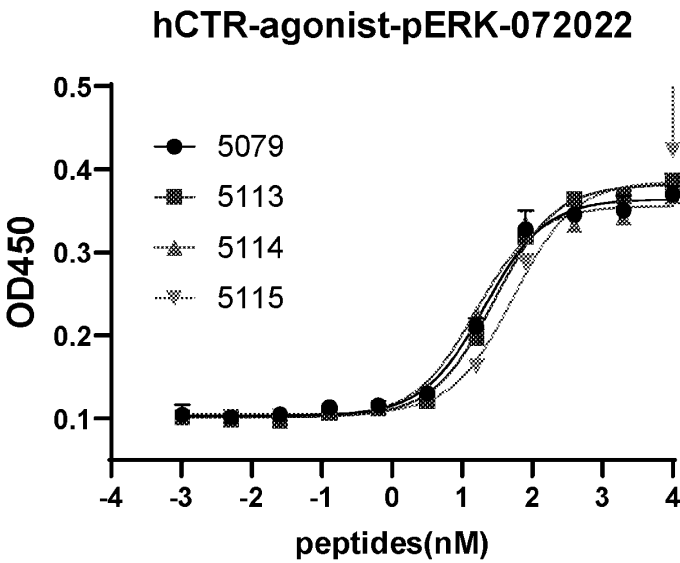


Fig. 5B

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5079 O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**X**ST-NVGSN-TP-NH₂
 5113 O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**X**ST-NVGSN-T**X**-NH₂
 5114 O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**X**ST-NVGSN-T**U**-NH₂
 5115 O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**X**ST-NVGSN-T**Z**-NH₂

O = (γE-COC18H32CO₂H)**X** = L,4-Hyp(Trans)**U** = Azetidine-2-carboxylic acid**Z** = Piperidine-2-carboxylic acid

Fig. 5C

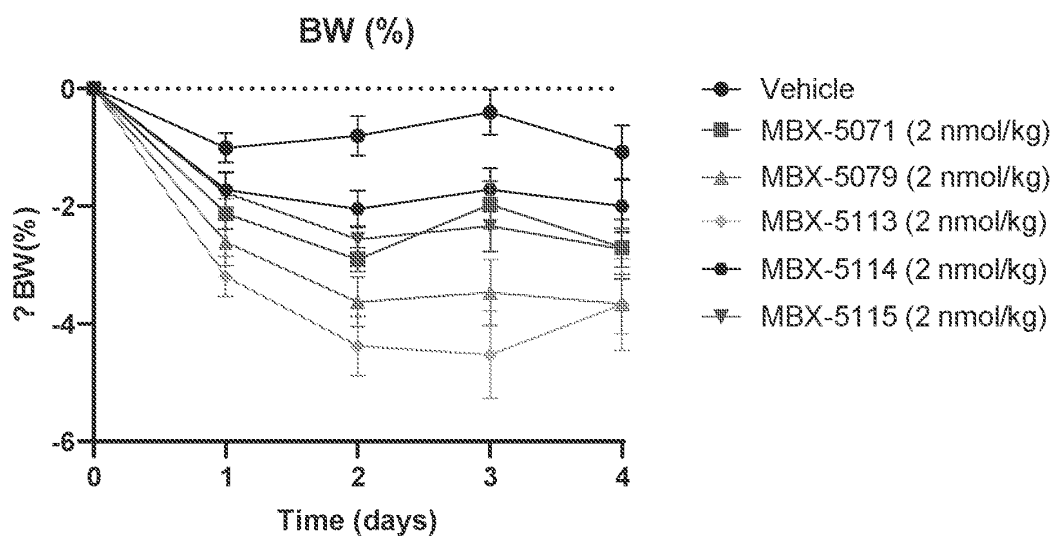


Fig. 6A

5071 O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGP-ILPPT-NVGSN-TP-NH₂
 5079 O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILXST-NVGSN-TP-NH₂
 5113 O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILXST-NVGSN-TX-NH₂
 5114 O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILXST-NVGSN-TU-NH₂
 5115 O-KCNTA-TCATQ-RLAEF-LRHSS-NNEGA-ILXST-NVGSN-TZ-NH₂

O = (γE-COC18H32CO₂H)

X = L, 4-Hyp(Trans)

U = Azetidine-2-carboxylic acid

Z = Piperidine-2-carboxylic acid

Fig. 6B

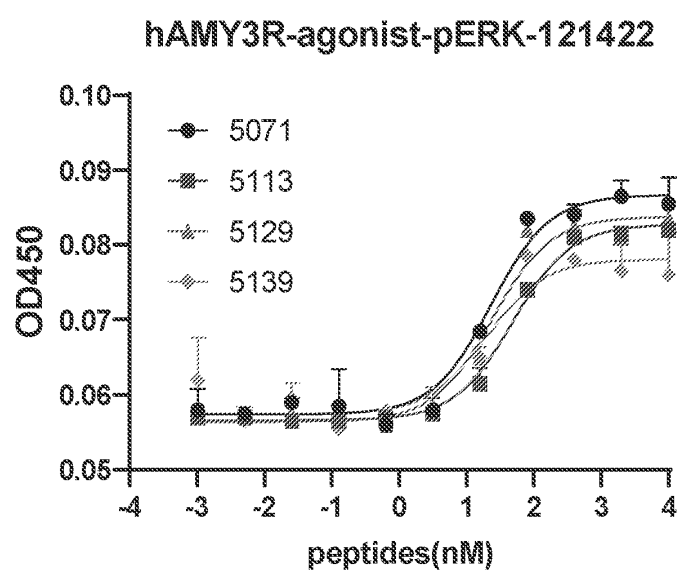


Fig. 7A

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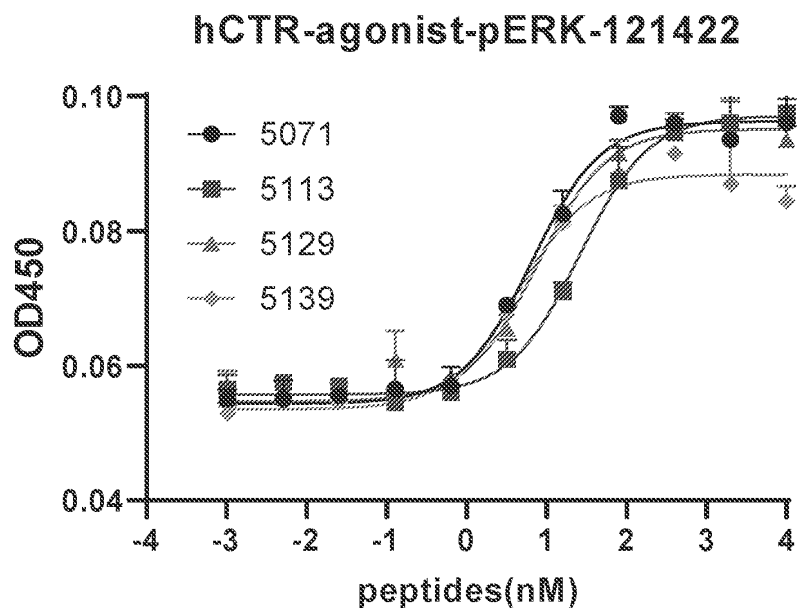


Fig. 7B

5071 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNFGP-ILPPT-NVGSN-TP-NH₂
 5079 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**X**ST-NVGSN-TP-NH₂
 5113 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**X**ST-NVGSN-**TX**-NH₂
 5114 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**X**ST-NVGSN-**TU**-NH₂
 5115 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNEGA-IL**X**ST-NVGSN-**TZ**-NH₂

O = (γE-COC18H32CO₂H)

X = L,4-Hyp(Trans)

U = Azetidine-2-carboxylic acid

Z = Piperidine-2-carboxylic acid

Fig. 7C

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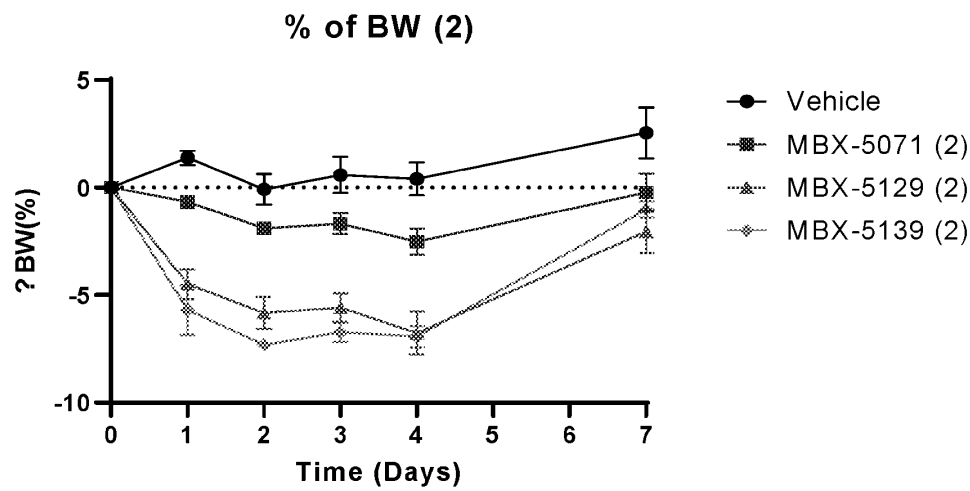


Fig. 8A

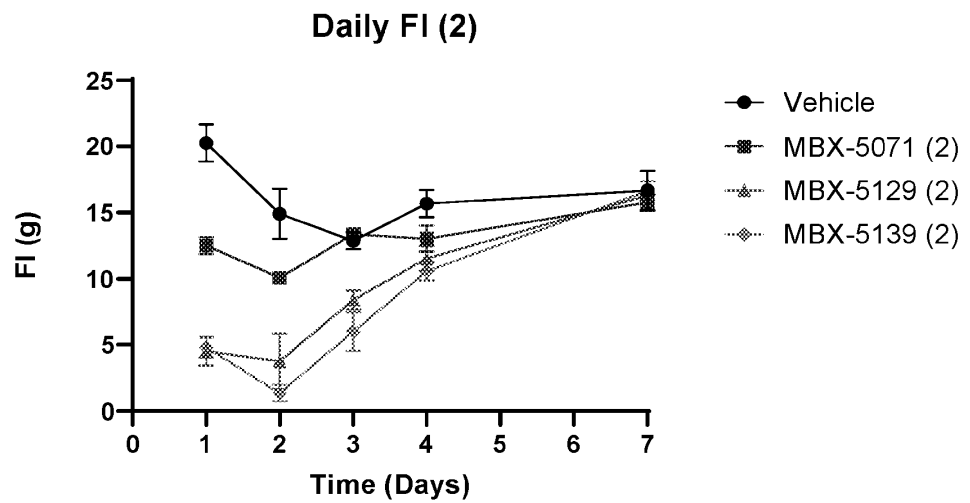


Fig. 8B

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MBX 5071: O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGP-ILPPT-NVGSN-TP-NH₂MBX 5129: O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH₂MBX 5139: O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZZT-NVGSN-TZ-NH₂O = (γE-COC18H32CO₂H)

Z = L,4-Hyp(Trans)

X = beta-lysine

Fig. 8C

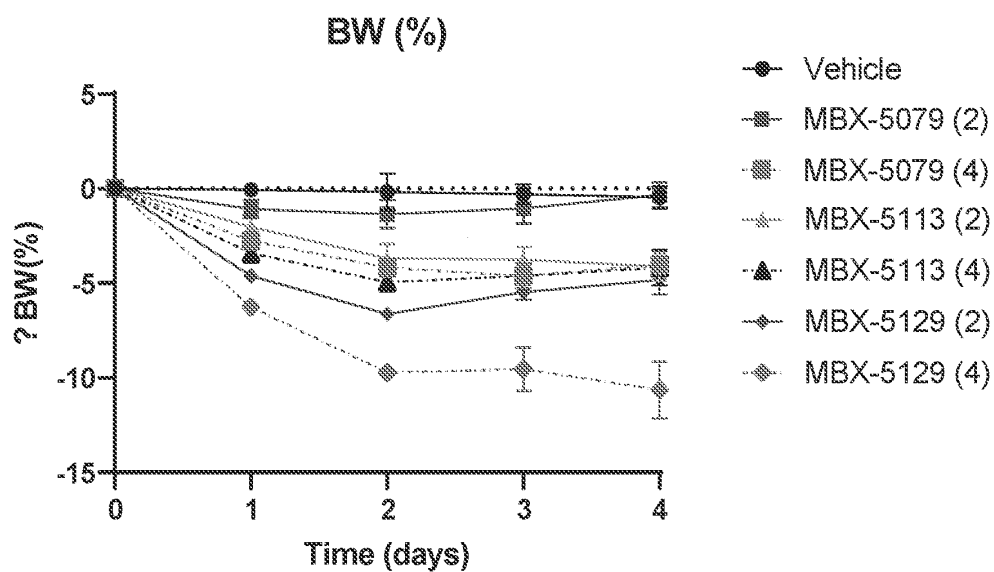


Fig. 9A

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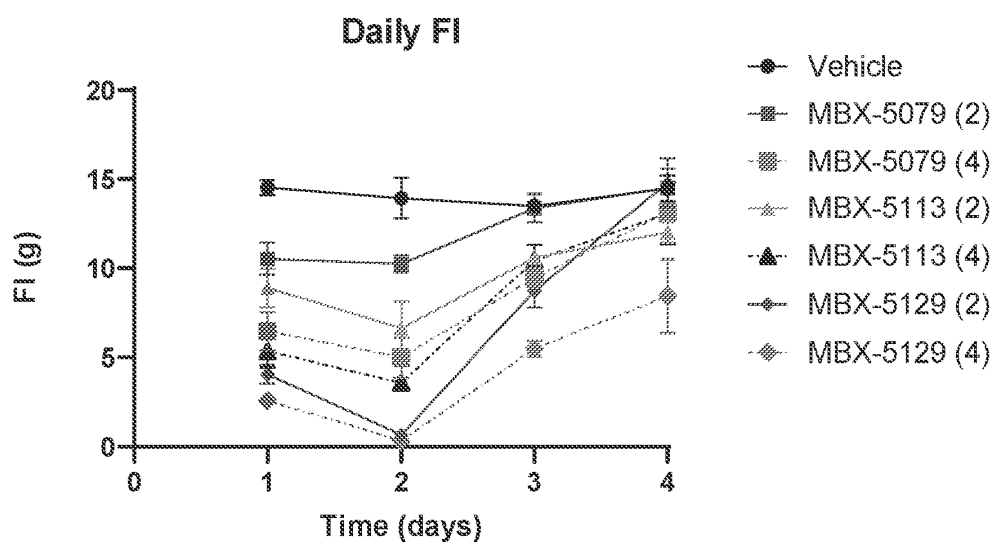


Fig. 9B

MBX 5079 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**Z**ST-NVGSN-TP-NH₂
 MBX 5113 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**Z**ST-NVGSN-T**Z**-NH₂
 MBX 5129 **O**-**X**CNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**Z****S**T-NVGSN-T**Z**-NH₂

O = (γE-COC18H32CO₂H)

Z = L, 4-Hyp (Trans)

X = beta-lysine

Fig. 9C

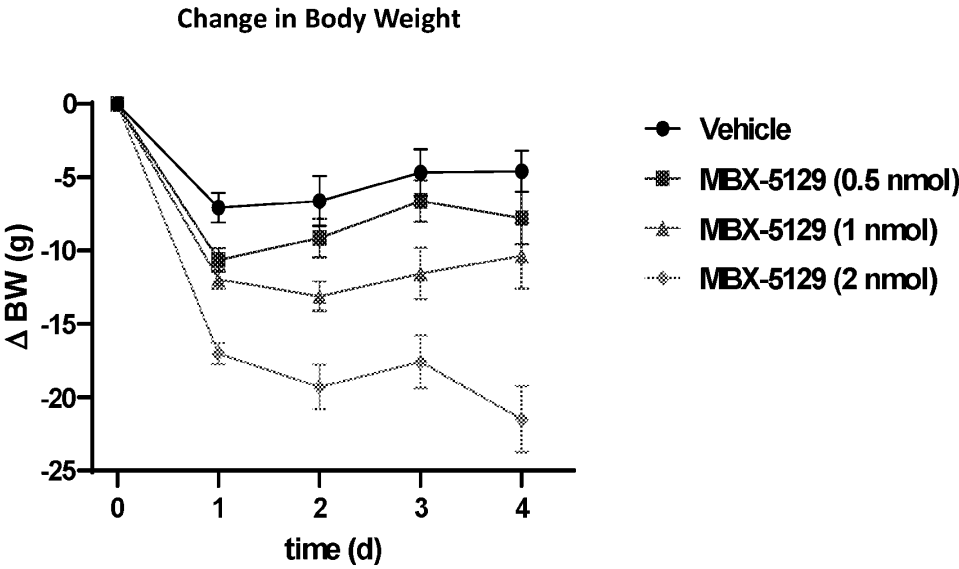


Fig. 10

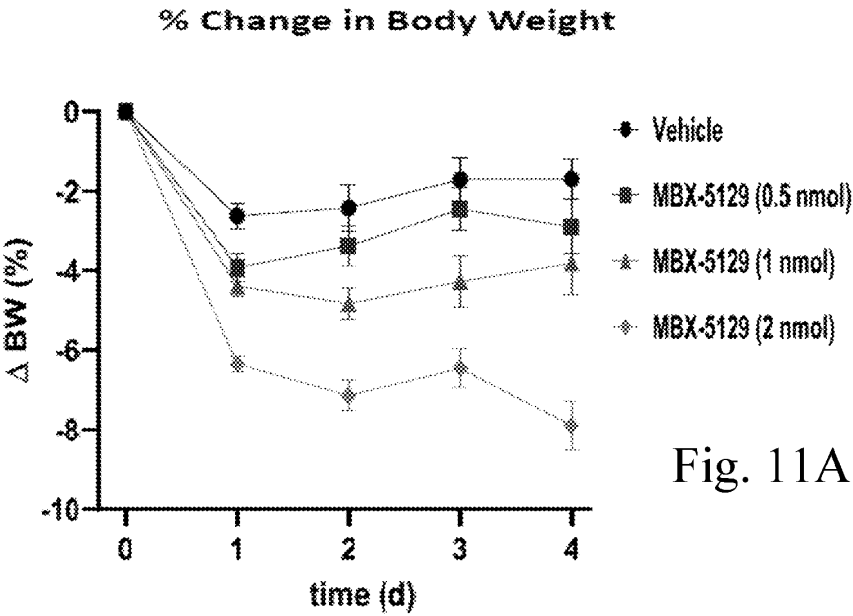


Fig. 11A

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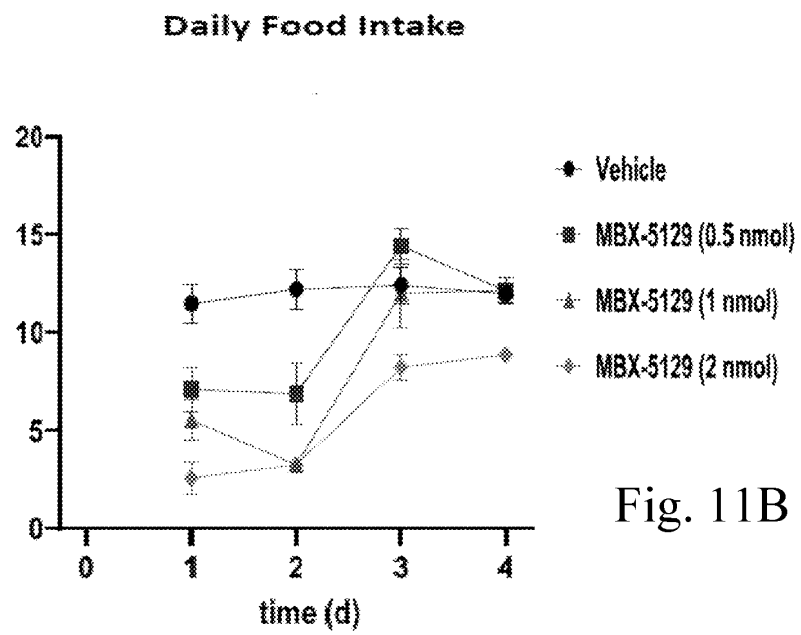


Fig. 11B

Fig. 12

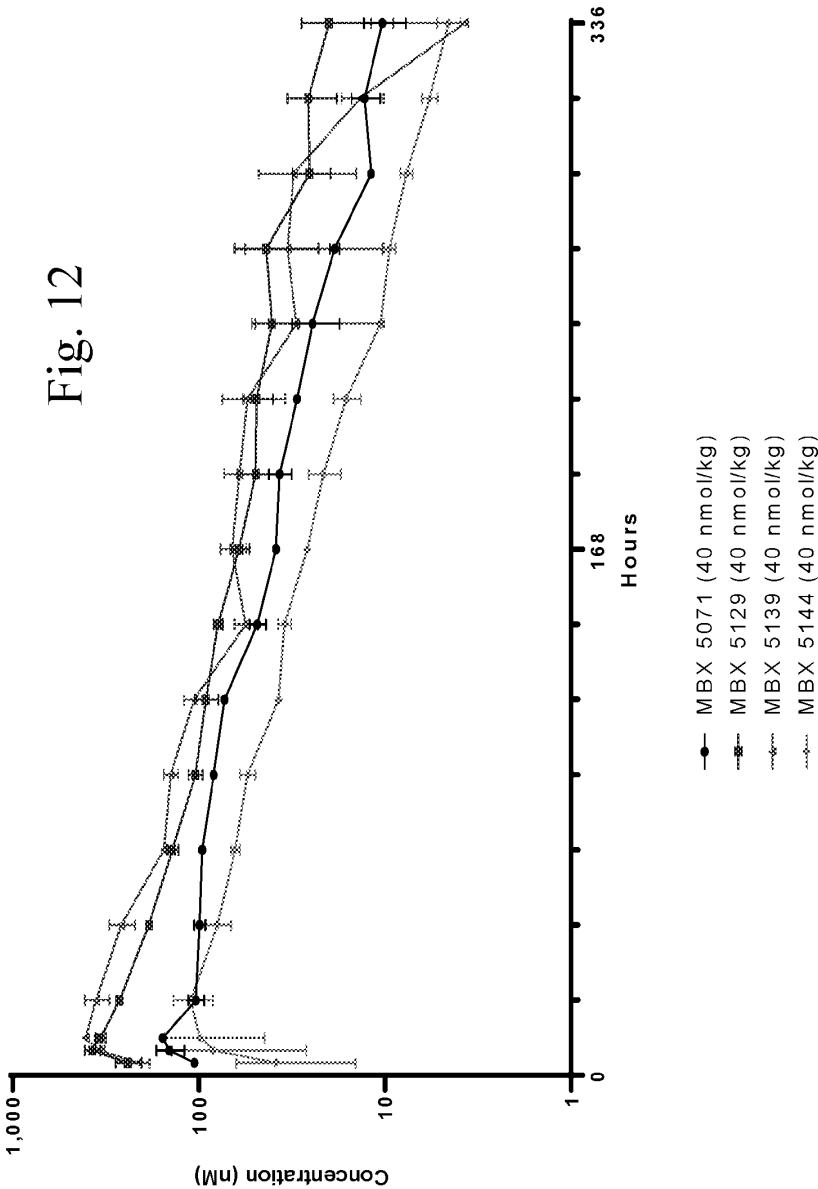


Fig. 13A

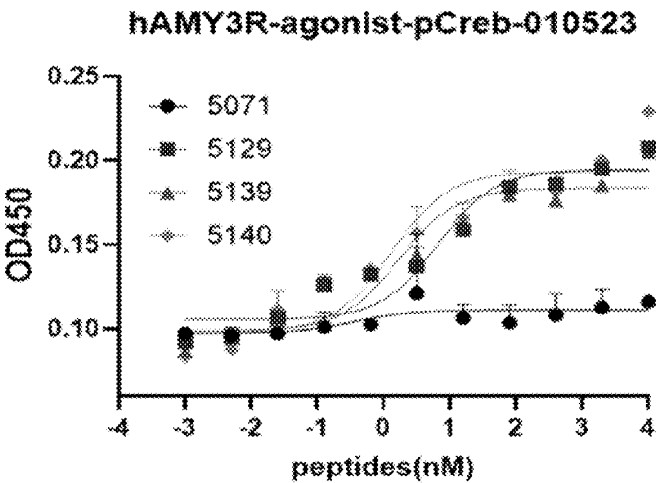
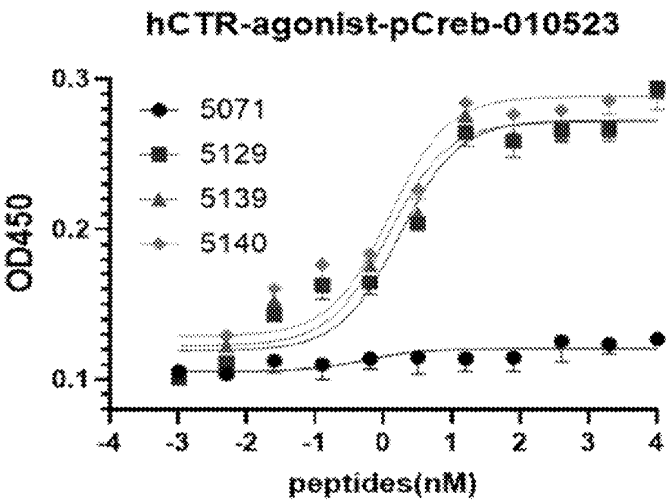


Fig. 13B



		5071	5129	5139	5140
EC50 (hAMY3R)		0.3371	6.647	1.699	1.334
EC50 (hCTR)		0.5258	1.724	1.202	1.225
O = (YE-CCC18H32CO2H)	5071	O-KCNTA-TCATQ-RLAEF-LRHSS-NNPGP-ILPPT-NVGSN-TP-NH2			
Z = L,4-Hyp (Trans)	5129	O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2			
U = L,3-Hyp (Trans)	5139	O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZZT-NVGSN-TZ-NH2			
X = beta, lysine	5140	O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILUUT-NVGSN-TZ-NH2			

Fig. 13C

Fig. 14A

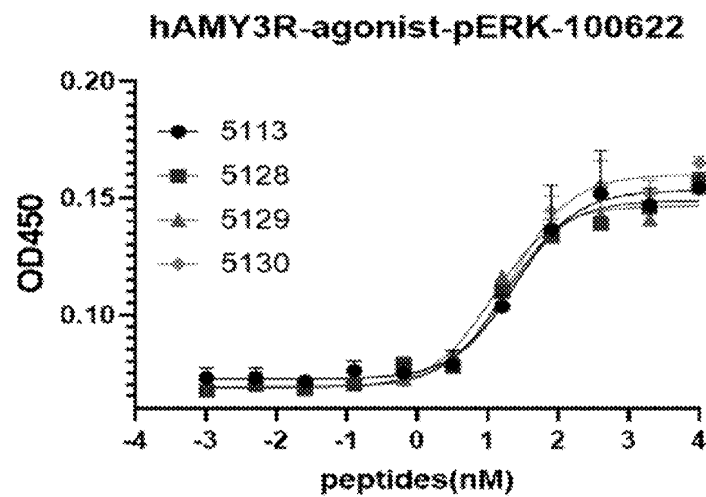
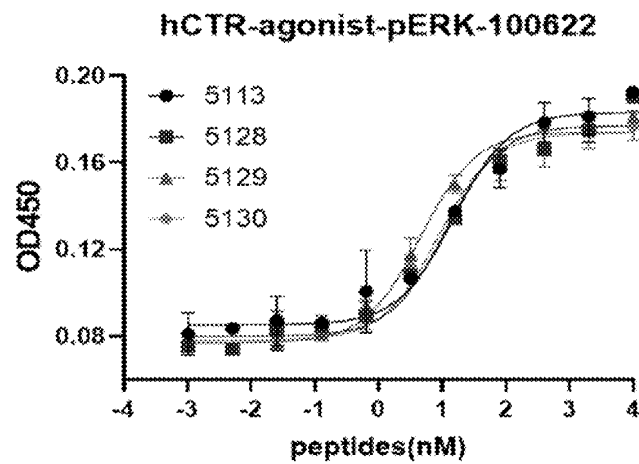


Fig. 14B



O = (VE-COC18H32CO2H)
Z = L, 4-Hyp (Trans)
k = D, lysine
X = beta, lysine
B = beta-D, lysine

51113 **O**-KCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**Z**ST-NVGSN-T**Z**-NH2
5128 **O**-**k**CNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**Z**ST-NVGSN-T**Z**-NH2
5129 **O**-**X**CNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**Z**ST-NVGSN-T**Z**-NH2
5130 **O**-**B**CNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**Z**ST-NVGSN-T**Z**-NH2

Fig. 14C

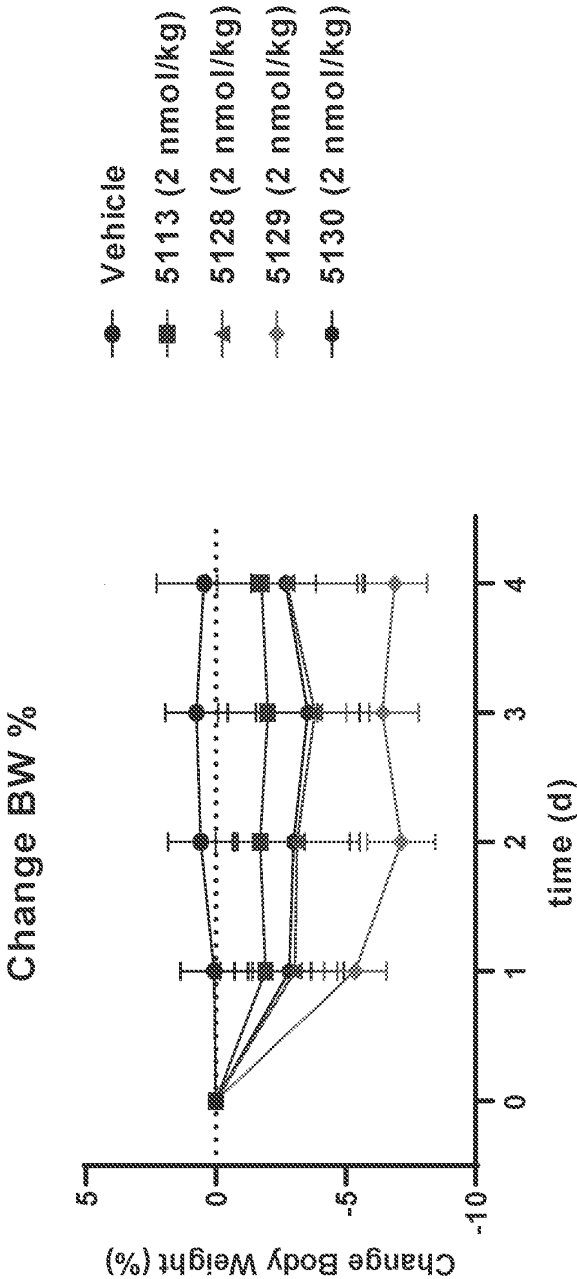


Fig. 15

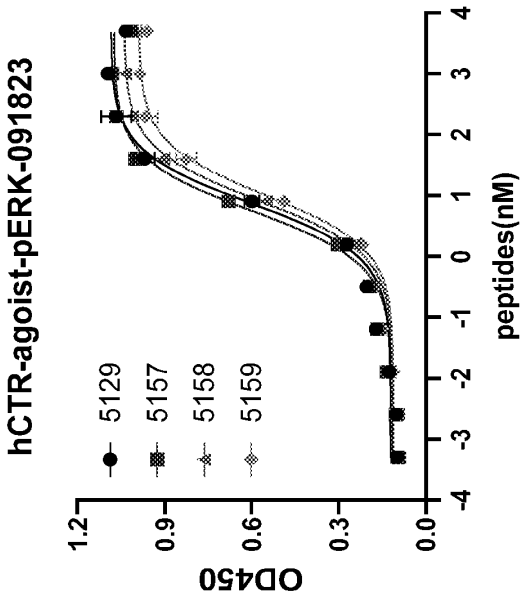


Fig. 16B

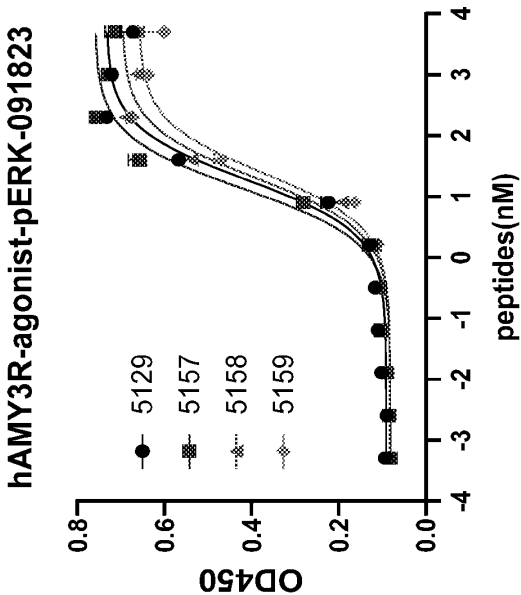


Fig. 16A

Ligands	5129	5157	5158	5159
EC50				
(hAMY3R)	18.96	13.45	20.03	23.88
	100	141	94.7	79.4
EC50				
(hCTR)	7.548	5.564	8.417	10.09
	100	135.7	89.7	74.8

Fig. 16C

5129	O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2
5157	O-XCNTS-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2
5158	O-XCNTA-TCATA-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2
5159	O-XCNTS-TCATA-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2

O = (γE-COC18H32CO2H)
Z = L,4-Hyp(Trans)
X = beta,lysine

Fig. 16D

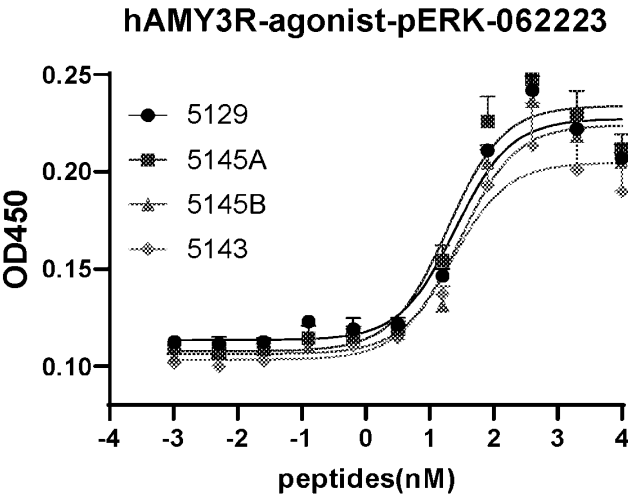


Fig. 17B

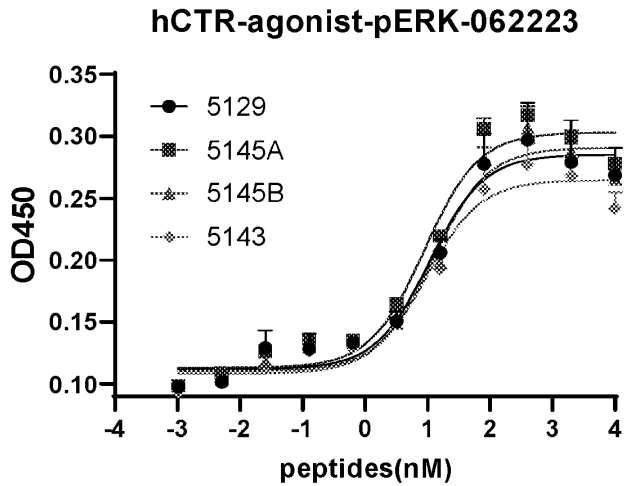


Fig. 17C

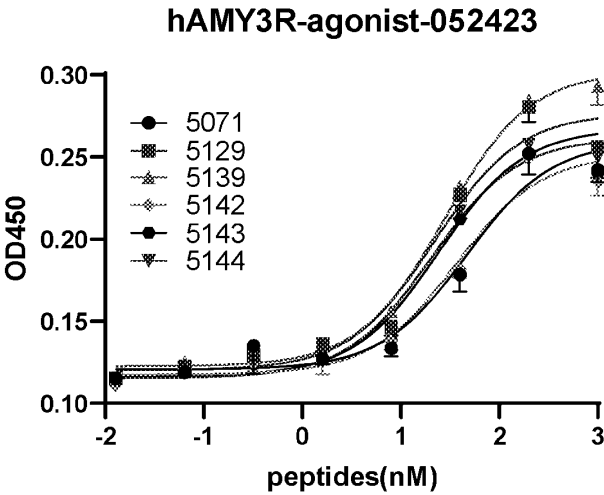


Fig. 18A

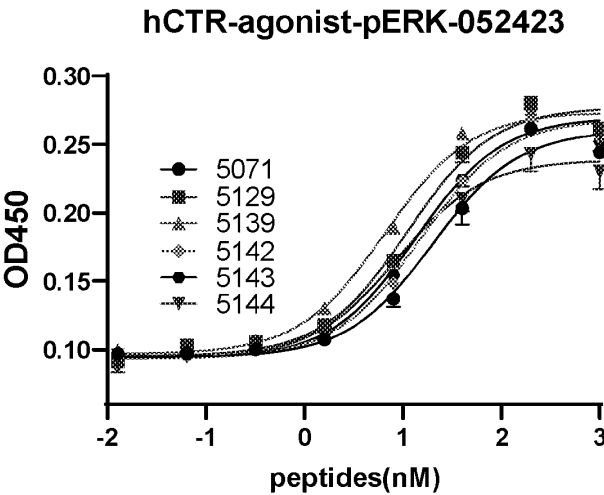


Fig. 18B

	5071	5129	5139	5142	5143	5144
EC50 (hCTR)	20.12	11.14	6.597	15.08	13.55	8.630
EC50 (hAMY3R)	46.67	21.89	27.85	36.22	24.34	20.40
5071	O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGP-ILPPT-NVGSN-TP-NH2					
5129	O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2					
5139	O-XNA-TCATQ-RLAEF-LRHSS-NNFGA-ILZZT-NVGSN-TZ-NH2					
5142	O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGP-ILPPT-NVGSN-TZ-NH2					
5143	O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILBST-NVGSN-TZ-NH2					
5144	O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGP-ILZZT-NVGSN-TZ-NH2					

O = (γE-COC18H32CO2H)
X = beta, lysine
Z = L, 4-Hyp(Trans)
B = L, 4-Hyp(Trans)acetyl, isoacyl

Fig. 18C

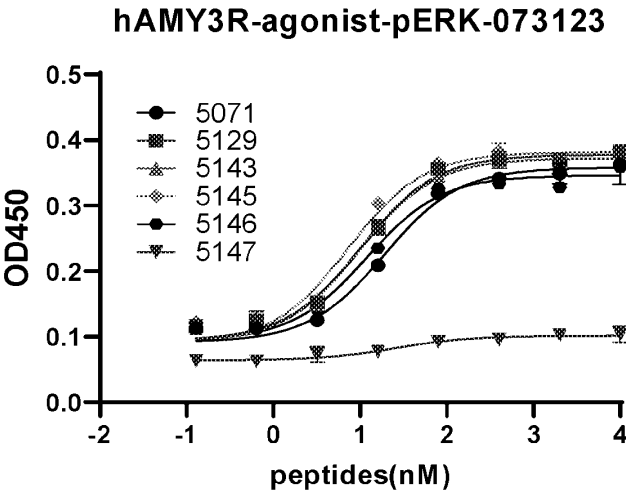


Fig. 19A

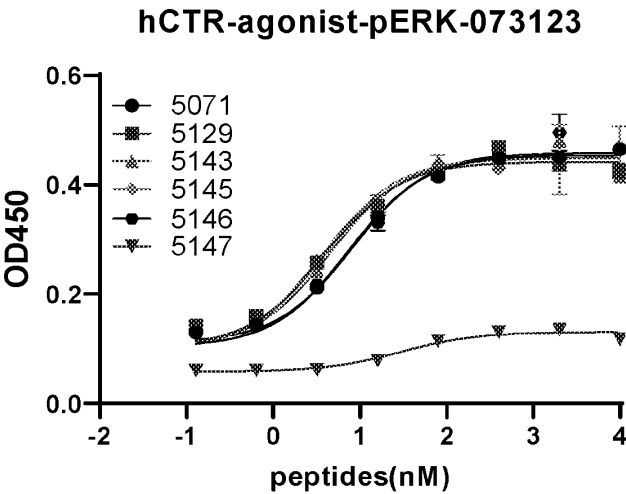


Fig. 19B

5071	O-KCNTA-TCATQ-RLAEF-LRHSS-NNFGP-ILPPT-NVGSN-TP-NH2
5129	O- XC NTA-TCATQ-RLAEF-LRHSS-NNFGA-IL Z ST-NVGSN- TZ -NH2
5143	O- XC NTA-TCATQ-RLAEF-LRHSS-NNFGA-IL B ST-NVGSN- TZ -NH2
5145	O- XC NTA-TCATQ-RLAEF-LRHSS-NNFGA-IL S B T-NVGSN- TZ -NH2
5146	O- XC NTA-TCATQ-RLAEF-LRH 1 S-NNFGA-IL Z ST-NVGSN- TZ -NH2
5147	O- XC NTA-TCA 2 Q-RLAEF-LRHSS-NNFGA-IL Z ST-NVGSN- TZ -NH2

O = (γE-COC18H32CO2H)
X = beta, lysine
Z = L, 4-Hyp(Trans)
B = L, Hyp(Trans), acetyl
1 = L, Ser, acetyl
2 = L, Thr, acetyl

Fig. 19C

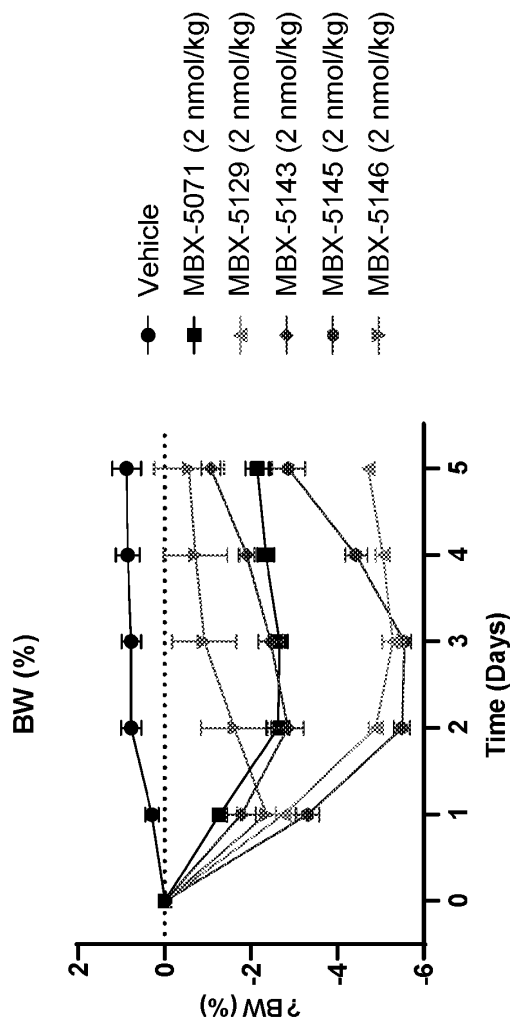


Fig. 20

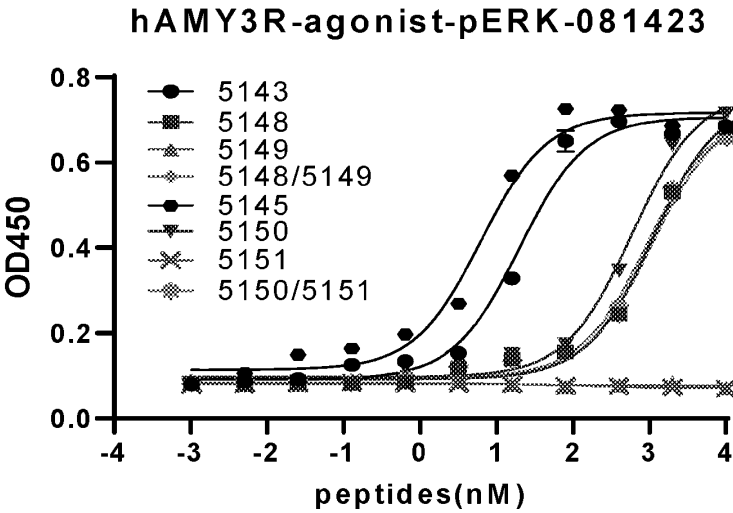


Fig. 21A

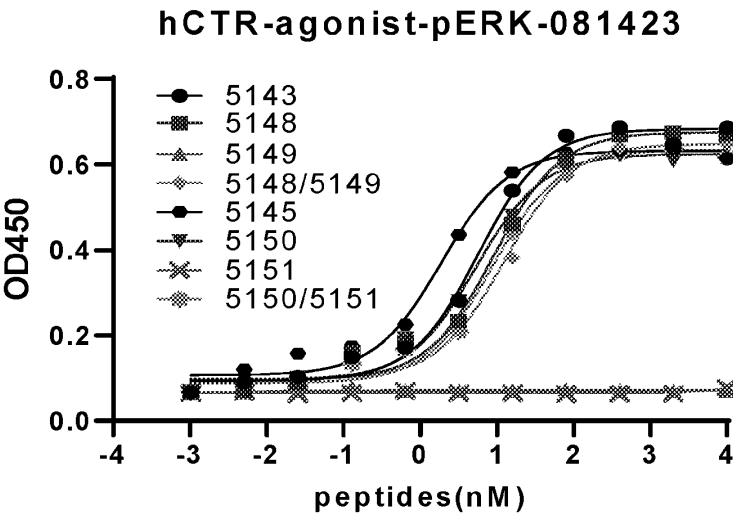
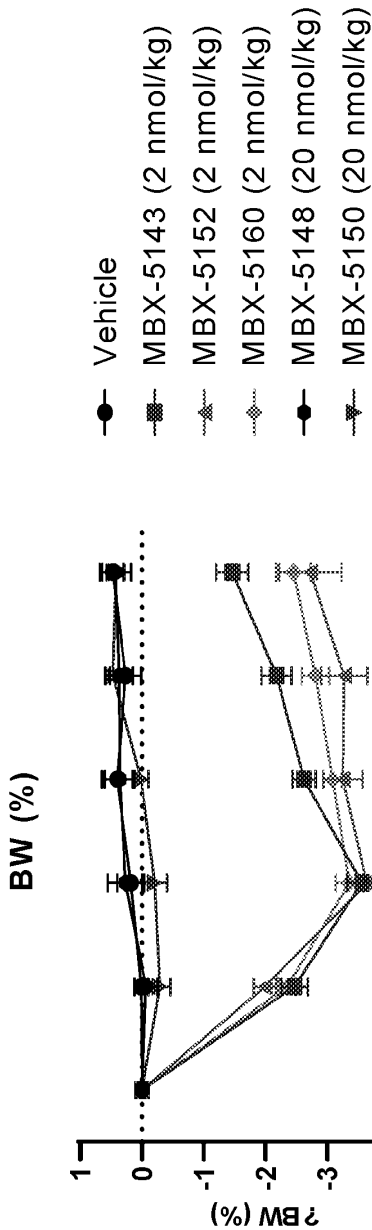


Fig. 21B

5143 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILBST-NVGSN-TZ-NH2
5148 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL-COOH
5149 BST-NVGSN-TZ-NH2
5145 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILSBT-NVGSN-TZ-NH2
5150 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILS-COOH
5151 BT-NVGSN-TZ-NH2

O = (γE-COC18H32CO2H)
Z = L,4-Hyp(Trans)
X = beta,lysine
B = L,Hyp(Trans),acetyl

Fig. 21C



5148 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL-COOH

5150 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILS-COOH

5160

5152 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILJST-NVGSN-TZ-NH2

5143 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILBST-NVGSN-TZ-NH2

O = (γE-COC18H32CO2H)

Z = L,4-Hyp (Trans)

X = beta, lysine

9 = L, ornithine, acetyl alpha amine

J = L,4-Hyp (Cis), acetyl

B = L,4-Hyp (Trans), acetyl

Fig. 22

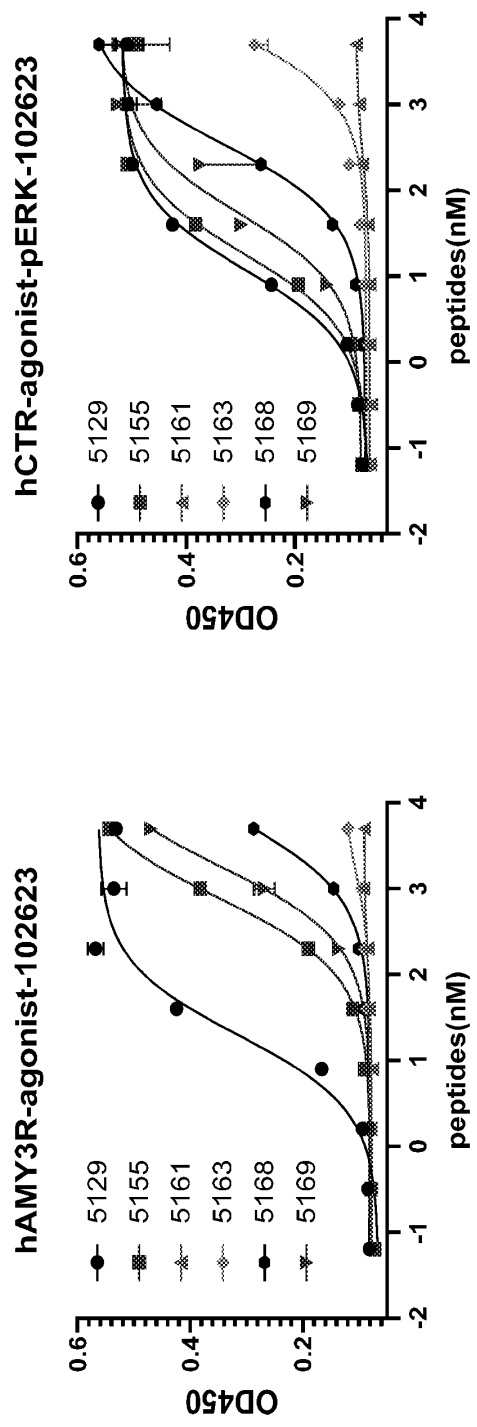


Fig. 23A

Fig. 23B

5129	O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2
5155	XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL-COOH
5169	XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-COOH
5168	XCNTA-TCATQ-RLAEF-LRHSS-COOH
5163	XCNTA-TCATQ-RLAEF-LRH-COOH
5161	XCNTA-TCA-COOH

O = (γE-COC18H32CO2H)
Z = L,4-Hyp (Trans)
X = beta, lysine

Fig. 23C

Ligands	5129	5155	5161	5163	5168	5169
EC50						
(hAMY3)	19.8	772.2	136	1603	5785	1803
% of 5129	100	2.6	14.6	1.2	0.3	1.1
EC50						
(hCTR)	11.86	18.3	220.8	10034	344.1	53.08
% of 5129	100	64.8	5.37	0.1	3.4	22.3

Fig. 23D

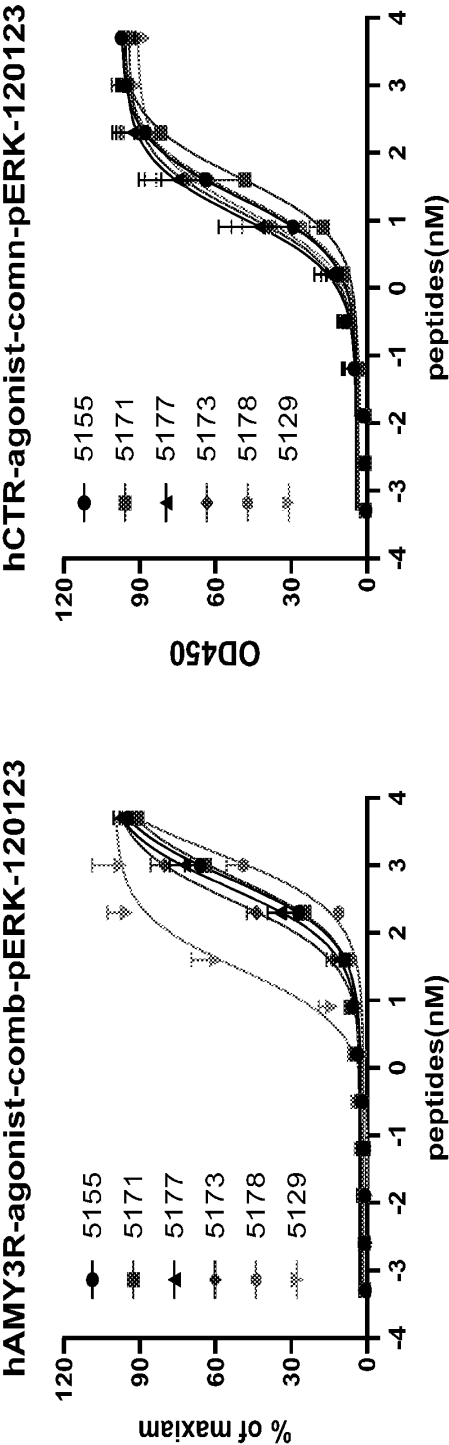


Fig. 24A

Fig. 24B

5155	XCNTA - TCATQ - RLAEF - LRHSS - NNFGA - IL - COOH	O = (γE-COC18H32CO2H)
5171	XCNTA - TCATQ - RLAEF - LRHSS - NNFGA - IL - NH2	Z = L, 4-Hyp (Trans)
5177	XCNTA - TCATQ - RLAEF - LRHSS - NNFGA - ILZST - NVGSN - COOH	X = beta, lysine
5173	XCNTA - TCATQ - RLAEF - LRHSS - NNFGA - ILZST - NVGSN - NH2	
5178	O-XCNTA - TCATQ - RLAEF - LRHSS - NNFGA - ILZST - NVGSN - TZ - COOH	
5129	O-XCNTA - TCATQ - RLAEF - LRHSS - NNFGA - ILZST - NVGSN - TZ - NH2	

Fig. 24C

Ligands	5155	5171	5177	5173	5178	5129
EC50 (hAMY3R)	638.3	672.2	468.4	288.9	1560	28.5
%	4.5	4.2	6.1	9.9	1.8	100
EC50 (hCTR)	22.04	43.29	11.23	12.78	23.17	13.45
%	61.0	31.1	119.8	105.2	58.0	100
Ratio	14	7	20	11	32	1

Fig. 24D

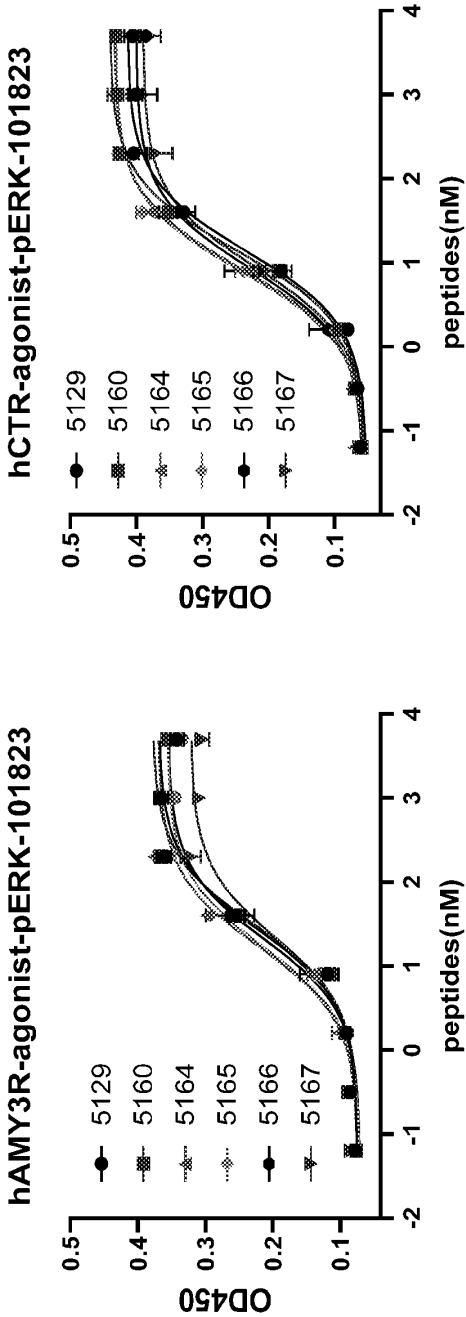


Fig. 25B

Fig. 25A

5129 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2

5160 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL1ST-NVGSN-TZ-NH2

5164 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL7ST-NVGSN-TZ-NH2

5165 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILJST-NVGSN-TZ-NH2

5166 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL8ST-NVGSN-TZ-NH2

5167 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL9ST-NVGSN-TZ-NH2

9 = PEG8-L, ornithine,
acetyl alpha amine

8 = PEG2-L, ornithine,
acetyl alpha amine

1 = L, ornithine,
acetyl alpha amine

7 = PEG2-L, 4-Hyp (Trans)

J = PEG8-L, 4-Hyp (Trans)

O = (γE-COC18H32CO2H)

Z = L, 4-Hyp (Trans)

X = beta, lysine

Fig. 25C

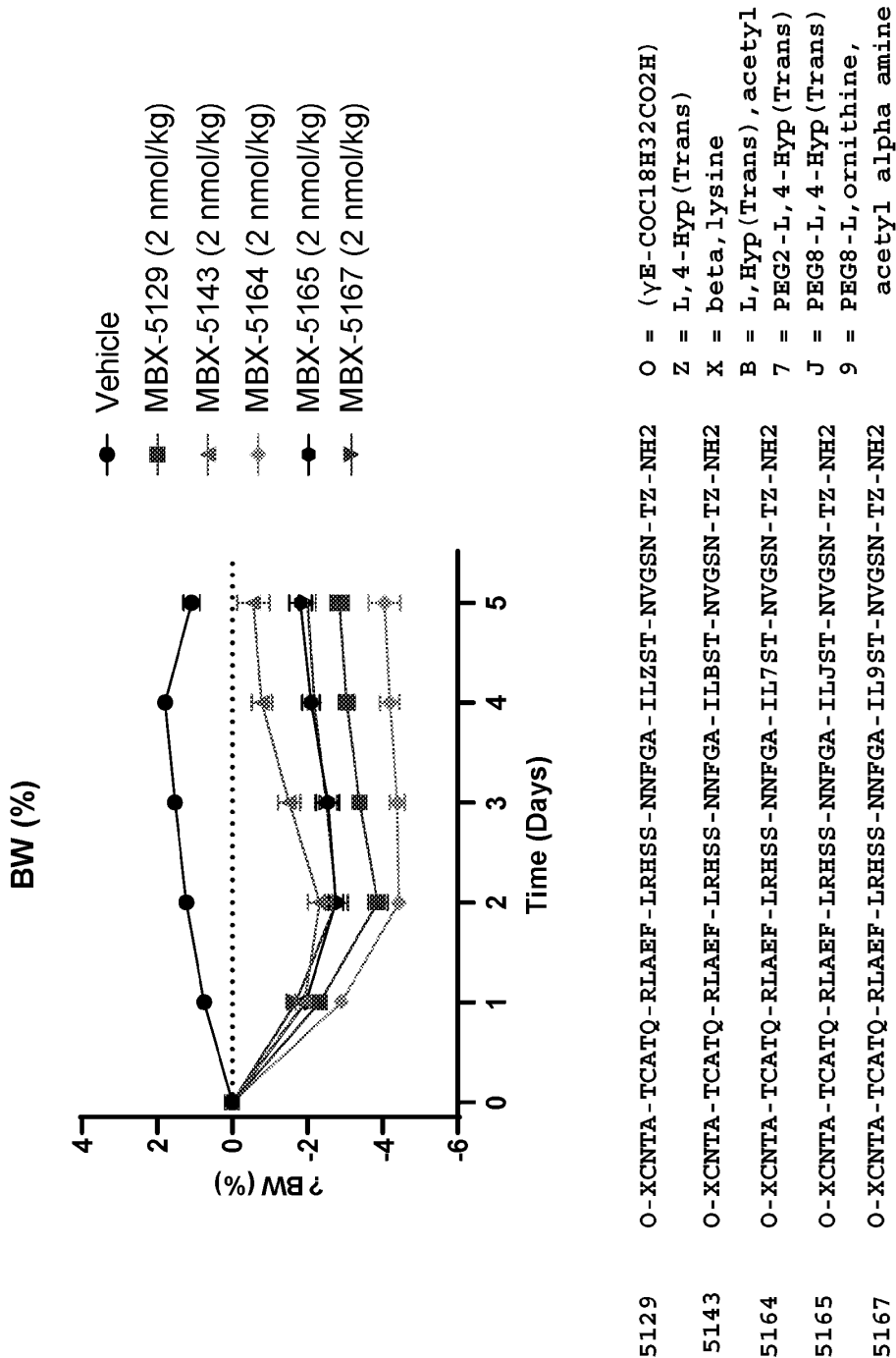


Fig. 26

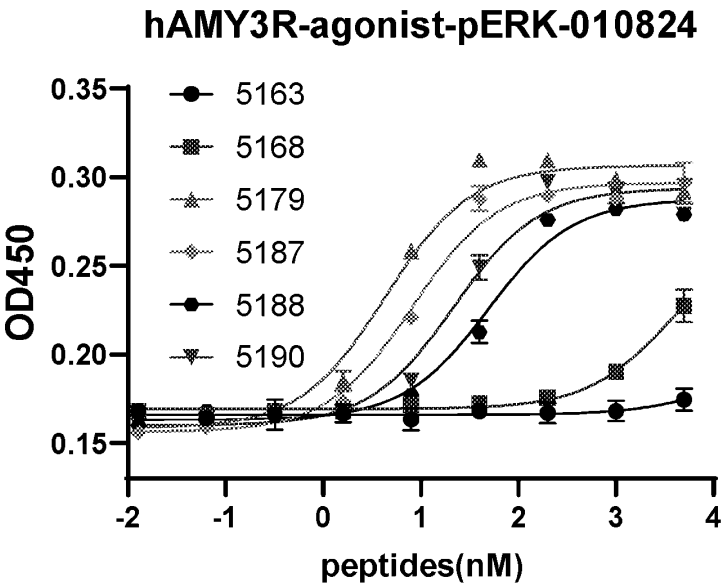


Fig. 27A

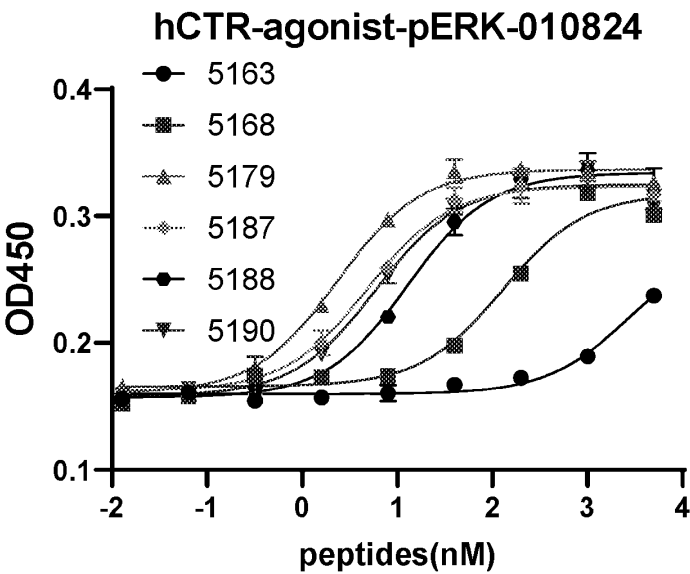


Fig. 27B

5163	XCNTA-TCATQ-RLAEF-LRH-COOH
5168	XCNTA-TCATQ-RLAEF-LRHSS-COOH
5179	XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2
5187	XCNTA-TCATQ-RLAEF-LRH-----UST-NVGSN-TZ-NH2
5188	O-XCNTA-TCATQ-RLAEF-LRH-----UST-NVGSN-TZ-NH2
5190	O-XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2

O = (γE-COC18H32CO2H)

Z = L, 4-Hyp (Trans)

X = beta, lysine

U = PEG10-L, 4-Hyp (Trans)

J = PEG8-L, 4-Hyp (Trans)

Fig. 27C

Ligands	5163	5168	5179	5187	5188	5190
EC50 (hAMY3R)	12879	3801	4.332	8.15	48.9	21.8
%	0.03	0.1	100	53.2	8.8	19.9
EC50 (hCTR)	2711	128.2	2.34	4.866	12.91	5.927
%	0.09	1.8	100	48.1	18.1	39.5

Fig. 27D

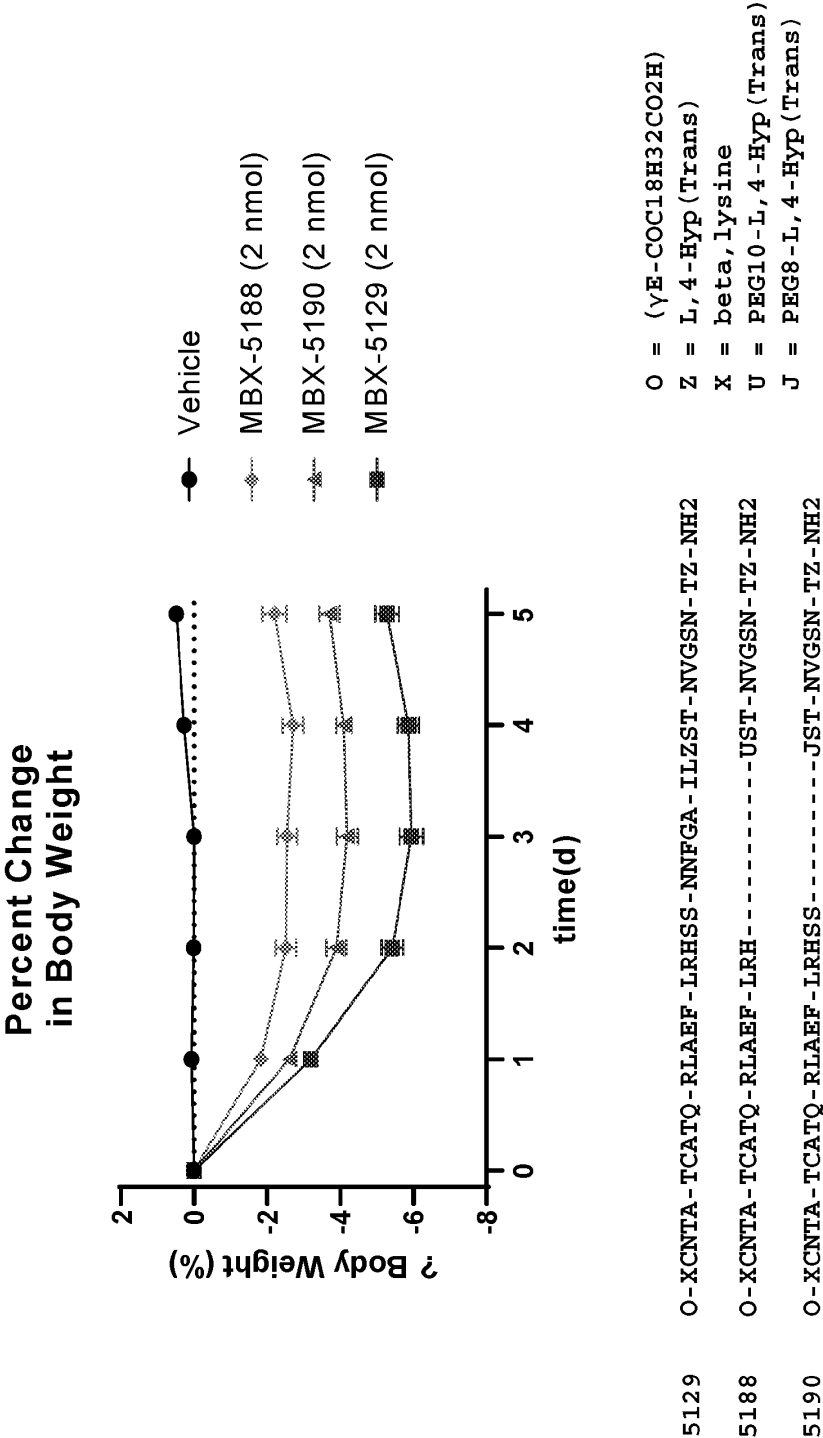


Fig. 28

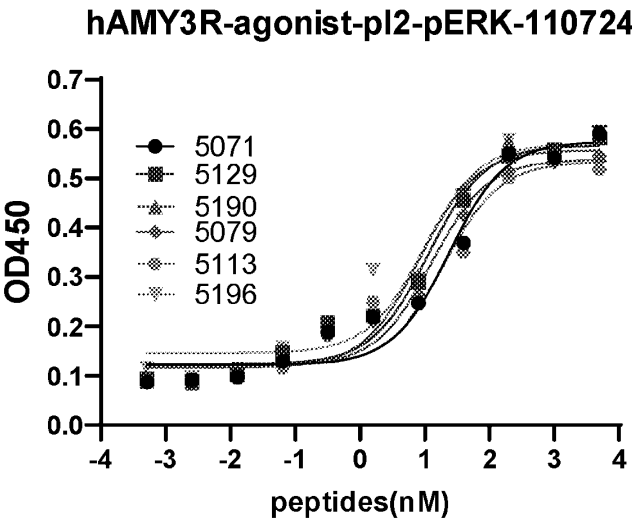


Fig. 29A

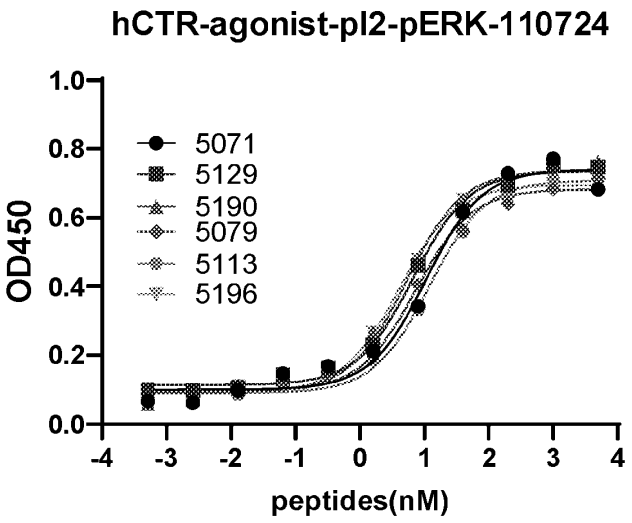


Fig. 29B

5079 O-KCNTA-TCATQ-RLAEF-LRHSS-NNEGA-ILZST-NVGSN-TP-NH2
5113 O-KCNTA-TCATQ-RLAEF-LRHSS-NNEGA-ILZST-NVGSN-TZ-NH2
5129 O-XCNTA-TCATQ-RLAEF-LRHSS-NNEGA-ILZST-NVGSN-TZ-NH2
5190 O-XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2
5196 O-XCNTA-TCATQ-RLAEF-LRHSS-----ZST-NVGSN-TZ-NH2
5071 O-KCNTA-TCATQ-RLAEF-LRHSS-NNEGP-ILPPT-NVGSN-TP-NH2

O = (VE-COC18H32CO2H)
Z = L, 4-Hyp (Trans)
X = beta, lysine
J = PEG8-L, 4-Hyp (Trans)

Fig. 29C

	5079	5113	5129	5190	5196	5071
hAMY3R	12.87	20.17	11.33	8.33	9.76	23.81
hCTR	7.34	11.91	6.72	5.28	4.09	10.66

Fig. 29D

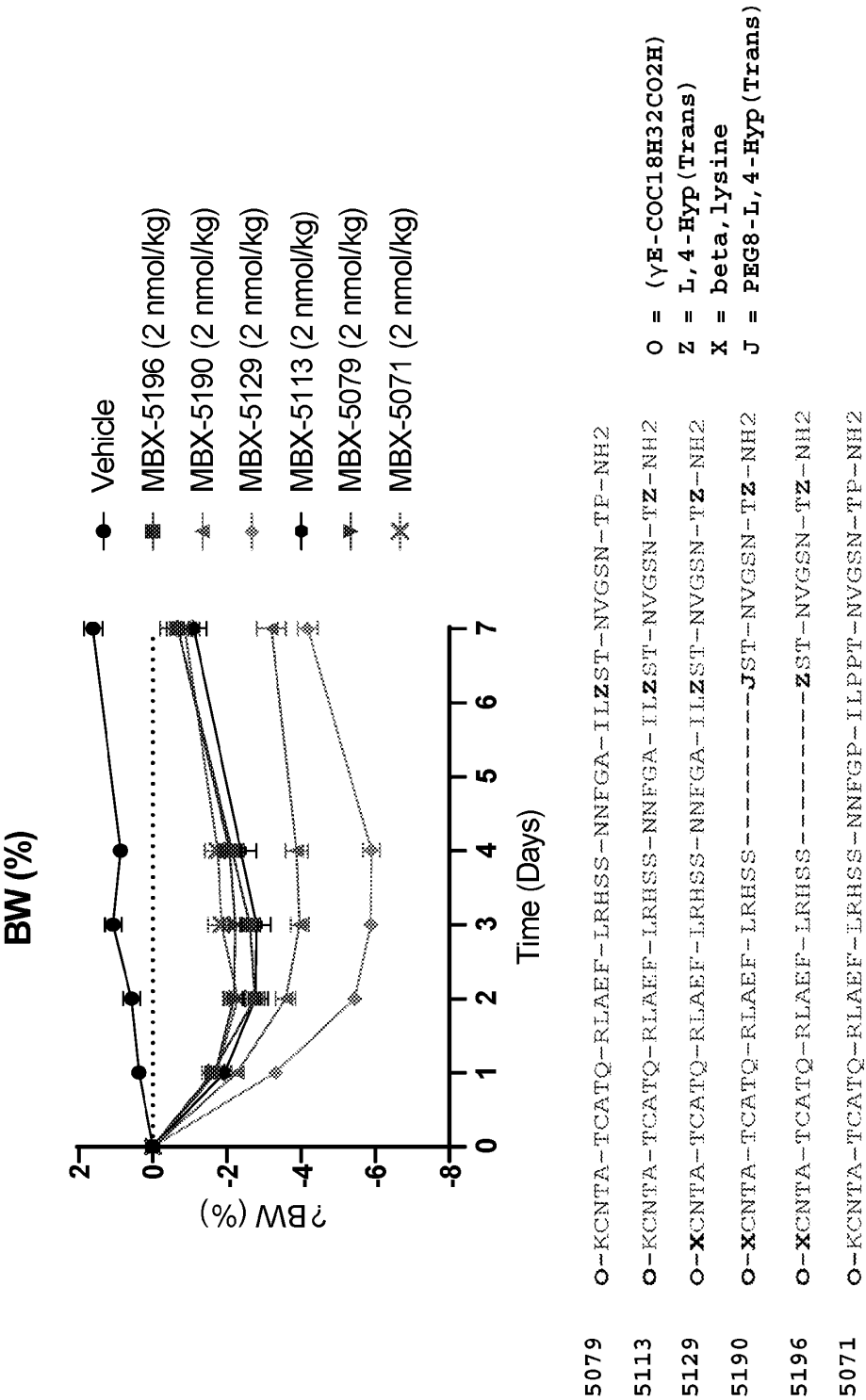


Fig. 30

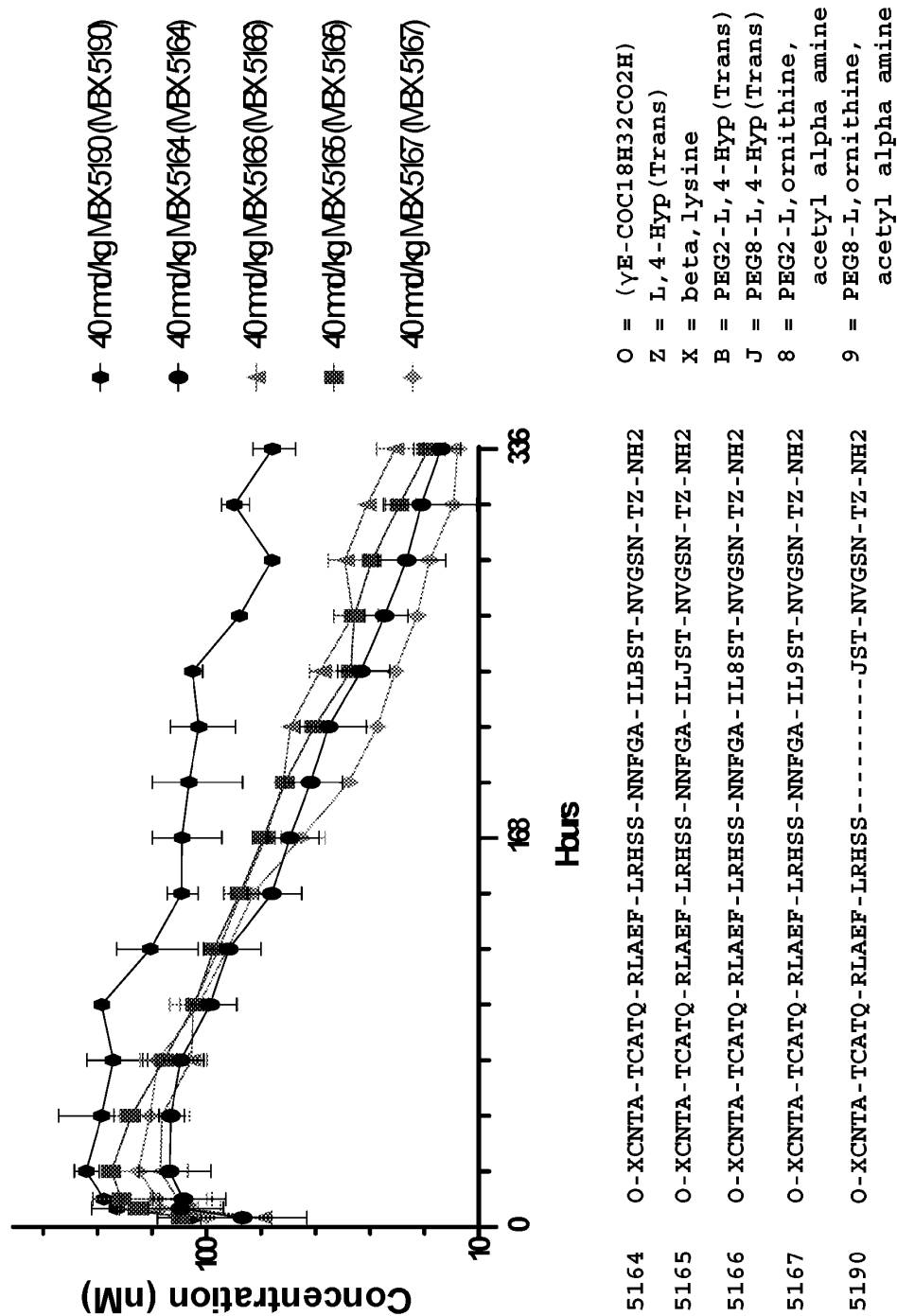


Fig. 31

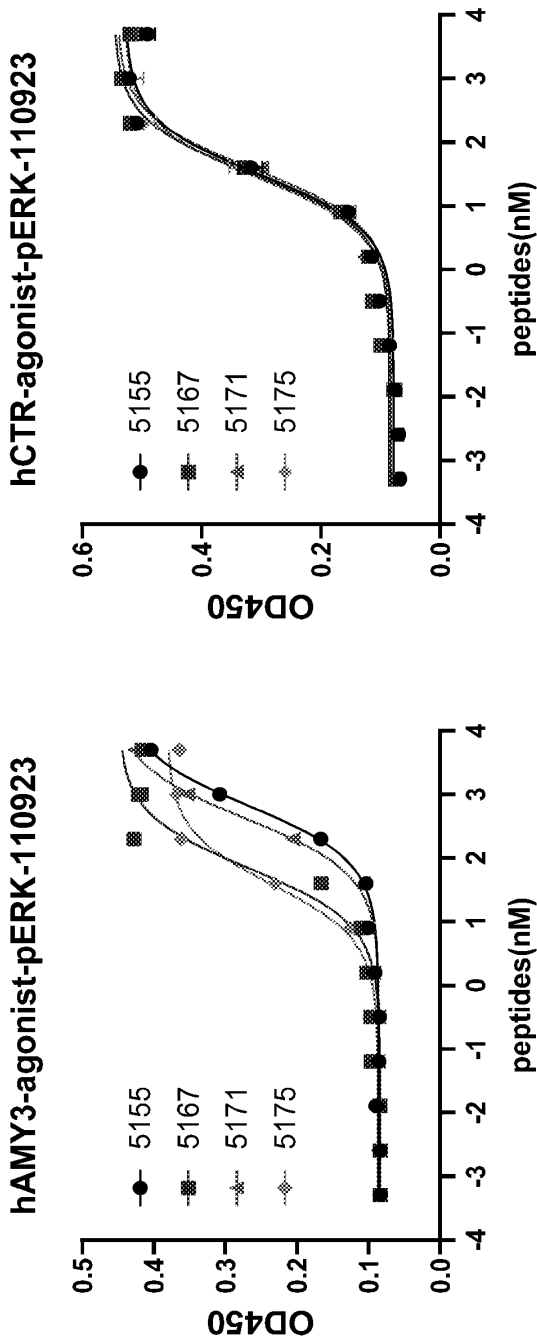


Fig. 33B

Fig. 33A

- 5155 XCNTA - TCATQ - RLAEF - LRHSS - NNFGA - IL - COOH
 - 5171 XCNTA - TCATQ - RLAEF - LRHSS - NNFGA - IL - NH₂
 - 5167 O - XCNTA - TCATQ - RLAEF - LRHSS - NNFGA - IL9ST - NVGSN - TZ - NH₂
 - 5175 XCNTA - TCATQ - RLAEF - LRHSS - NNFGA - IL7ST - NVGSN - TZ - NH₂
- O = (VE-COC18H32CO2H)
Z = L, 4-HVP (Trans)
X = beta-lysine
9 = Ac-Orn(Peg8) with O-X-Amylin (2-27) acylated through delta amine
7 = Semaglutide-Peg8 (no lipid) acylated to alpha amine of Orn,
and X-Amylin (2-27) (Peg8) acylated to delta amine

Fig. 33C

Ligands	5155	5167	5171	5175
EC50 (hAMY3R)	661.5	68.9	417.8	38.18
%	100	960	158	1732
EC50 (hCTR)	31.07	31.92	37.69	27.83
%	100	97	82	112

Fig. 33D

hGLP-1R Transfected Cells

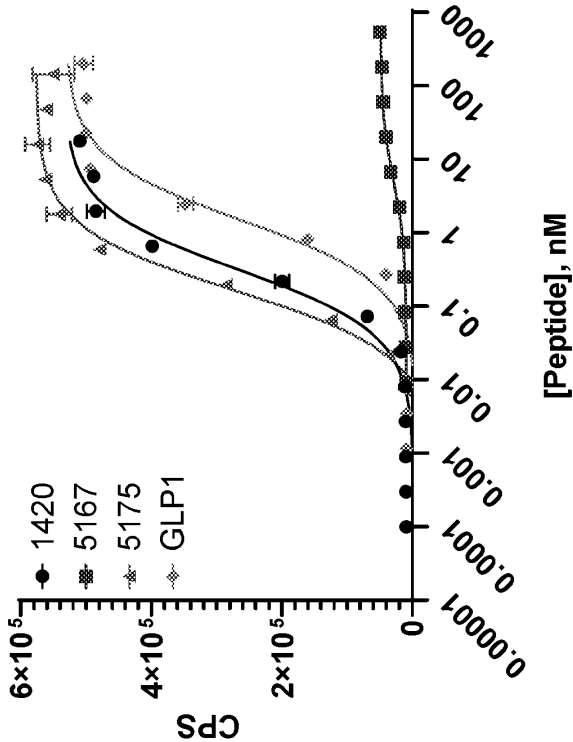


Fig. 34A

O = (VE-COC18H32CO2H)
Z = L, 4-HYP (Trans)
X = beta-lysine
9 = Ac-Orn with O-X-Amylin (2-27) (Peg8) acylated through delta amine
7 = Semaglutide-Peg8 (no lipid) acylated to alpha amine of Orn, and X-Amylin (2-27) (Peg8) acylated to delta amine

	Structure	EC50	% GLP-1
Standard	GLP-1	1.42	100
1420	Semaglutide	0.29	495
5167	O--XCNTA--TCATQ--RLAEF--LRHSS--NNEGA--IL9ST--NVGSN--TZ--NH2	-	-
5175	XCNTA--TCATQ--RLAEF--LRHSS--NNEGA--IL7ST--NVGSN--TZ--NH2	0.18	770

Fig. 34B

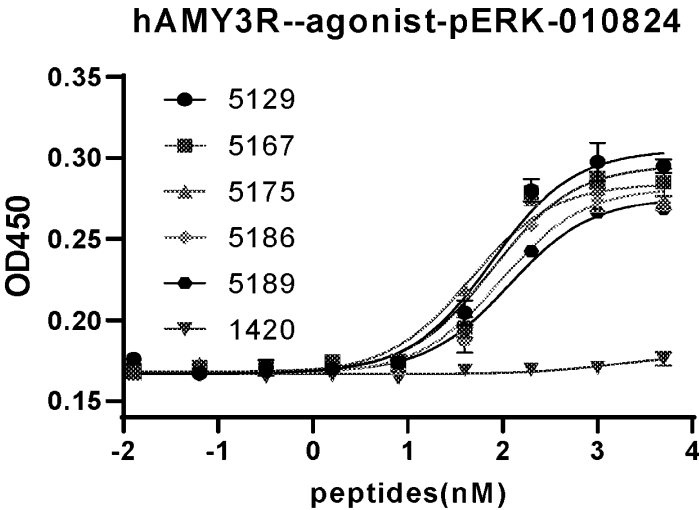


Fig. 35A

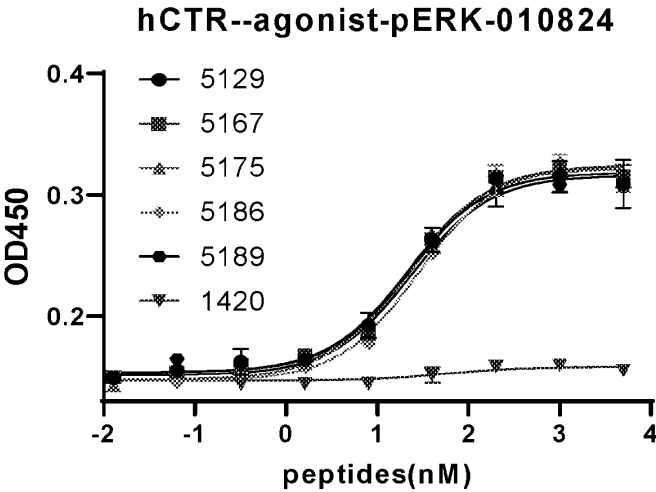


Fig. 35B

5167 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL6ST-NVGSN-TZ-NH2
5175 XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL7ST-NVGSN-TZ-NH2
5186 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL8ST-NVGSN-TZ-NH2
5189 XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL9ST-NVGSN-TZ-NH2
1420 HJEGT-FTSDV-SSYLE-GQAAK-UEFIA-WLVRG-RG-OH

O = (vE-COC18H32CO2H)
X = beta-lysine
Z = L, 4-HYP (Trans)
6 = Ac-Orn with O-X-Amylin (2-27) (Peg8) acylated through delta amine
7 = Semaglutide-Peg8 (no lipid) acylated to alpha amine of Orn, and X-Amylin (2-27) (Peg8) acylated to delta amine
8 = Semaglutide-Peg8 (no lipid) acylated to alpha amine of Orn, and O-X-Amylin (2-27) (Peg8) acylated to delta amine
9 = Semaglutide-Peg8 (lipid) acylated to alpha amine of Orn, and X-Amylin (2-27) (Peg8) acylated to delta amine
J = Aib
U = mPeg, mPeg, rE(C18 diacid)

Fig. 35C

Fig. 35D

Ligands	5129	5167	5175	5186	5189	1420
EC50 (hAMY3R)	76.65	78.59	46.25	95.13	115.9	-
%	100	97.5	165.7	80.6	66.1	-
EC50 (hCTR)	21.24	24.02	20.59	28.21	23.4	-
%	100	88.4	103.2	75.3	90.8	-

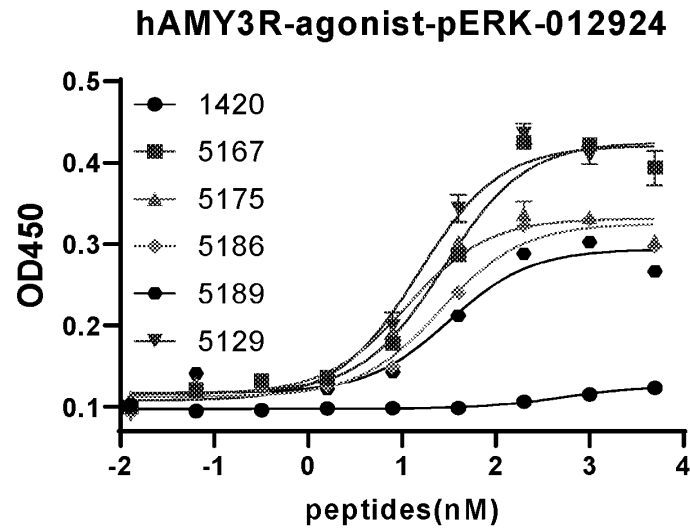


Fig. 36A

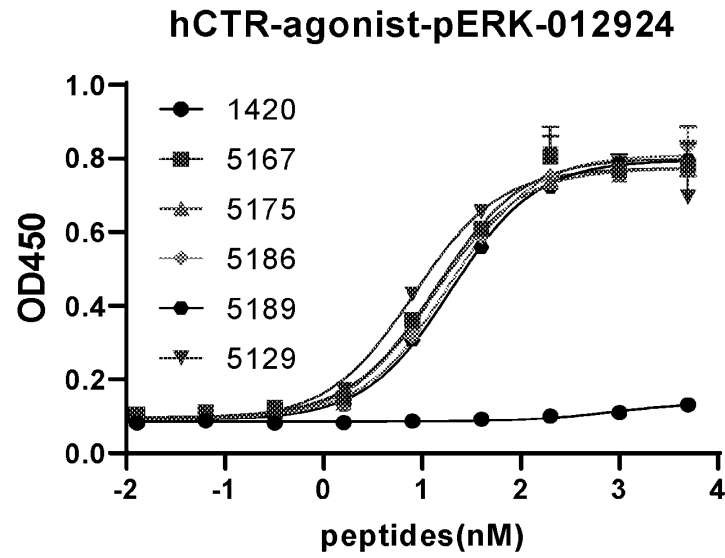


Fig. 36B

5167 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL6ST-NVGSN-TZ-NH2
5175 XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL7ST-NVGSN-TZ-NH2
5186 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL8ST-NVGSN-TZ-NH2
5189 XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL9ST-NVGSN-TZ-NH2
5129 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2
1420 HJEGT-FTSDV-SSYLE-GQAAK-UEFIA-WLVRG-RG-OH

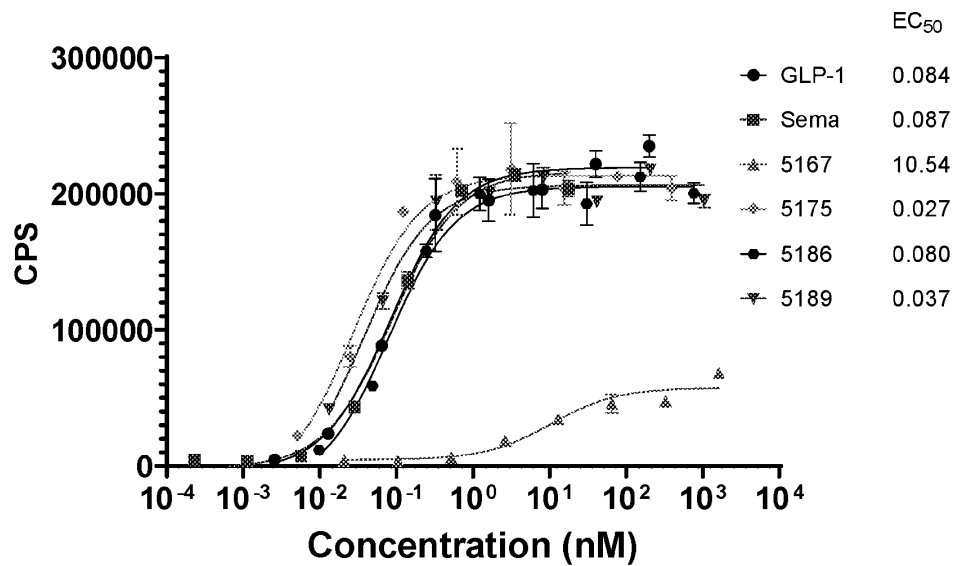
Fig. 36C

O = (vE-COC18H32CO2H)
X = beta-lysine
Z = L, 4-HYP (Trans)
6 = Ac-Orn with O-X-Amylin (2-27) (Peg8) acylated through delta amine
7 = Semaglutide-Peg8 (no lipid) acylated to alpha amine of Orn, and X-Amylin (2-27) (Peg8) acylated to delta amine
8 = Semaglutide-Peg8 (no lipid) acylated to alpha amine of Orn, and O-X-Amylin (2-27) (Peg8) acylated to delta amine
9 = Semaglutide-Peg8 (lipid) acylated to alpha amine of Orn, and X-Amylin (2-27) (Peg8) acylated to delta amine
J = Aib
U = mPeg, mPeg, rE(C18 diacid)

Ligands	1420	5167	5175	5186	5189	5129
EC50 (hAMY3R)	-	27.81	11.17	25.94	31.77	15.04
%	-	54.1	134.6	58	47.3	100
EC50 (hCTR)	-	13.77	13.28	18.43	19.62	8.27
%	-	60.1	62.3	44.9	42.2	100

Fig. 36D

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5167 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL6ST-NVGSN-TZ-NH2
5175 XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL7ST-NVGSN-TZ-NH2
5186 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL8ST-NVGSN-TZ-NH2
5189 XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL9ST-NVGSN-TZ-NH2
1420 HJEGT-FTSDV-SSYLE-GQAAK-UEFIA-WLVRG-RG-OH

Fig. 37

O = (γE-COC18H32CO2H)

X = beta-lysine

Z = L, 4-HYP (Trans)

6 = Ac-Orn with O-X-Amylin (2-27) (Peg8) acylated through delta amine

7 = Semaglutide-Peg8 (no lipid) acylated to alpha amine of Orn, and X-Amylin (2-27) (Peg8) acylated to delta amine

8 = Semaglutide-Peg8 (no lipid) acylated to alpha amine of Orn, and O-X-Amylin (2-27) (Peg8) acylated to delta amine

9 = Semaglutide-Peg8 (lipid) acylated to alpha amine of Orn, and X-Amylin (2-27) (Peg8) acylated to delta amine

J = Aib

U = mPeg, mPeg, rE(C18 diacid)

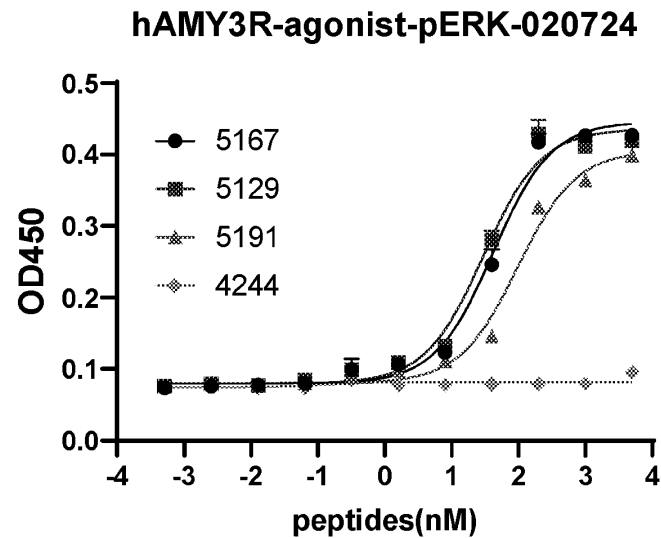


Fig. 38A

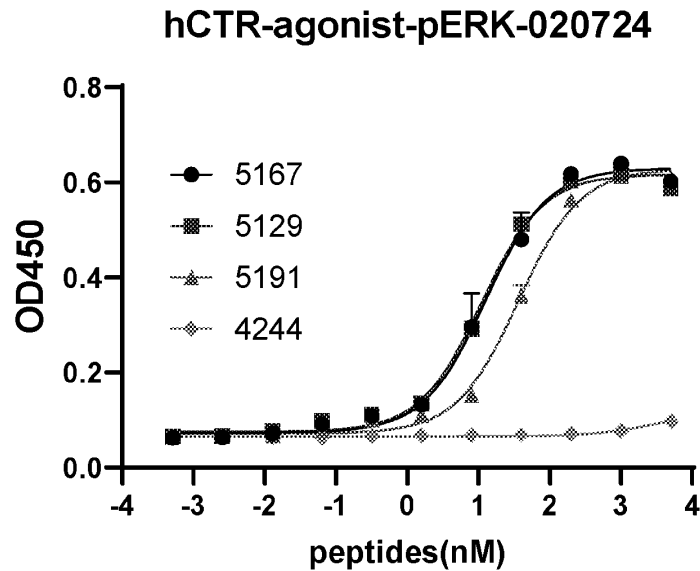


Fig. 38B

5167 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL9ST-NVGSN-TZ-NH2

5191 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL6ST-NVGSN-TZ-NH2

5129 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2

4244 YJQGTFTSDYSIBLDK8AQJAFIEYLLLEGGPSSGAPPPS-NH2

Fig. 38C

O = (γE-COC18H32CO2H)

X = beta-lysine

Z = L, 4-HYP (Trans)

9 = Ac-Orn with O-X-Amylin (2-27) (Peg8) acylated through delta amine

6 = Retatrutide-Peg8 (no lipid) acylated to alpha amine of Orn, and O-X-Amylin (2-27) (Peg8) acylated to delta amine

J = Aib

B = alpha, methyl Leu

8 = K(miniPEG-γE-COC18H36CO2H)

Fig. 38D

Ligands	5167	5129	5191	4244
EC50 (hAMY3R)	41.78	29.77	98.06	-
%	71.3	100	30.4	-
EC50 (hCTR)	12.59	11.06	36.49	-
%	87.8	100	30.3	-

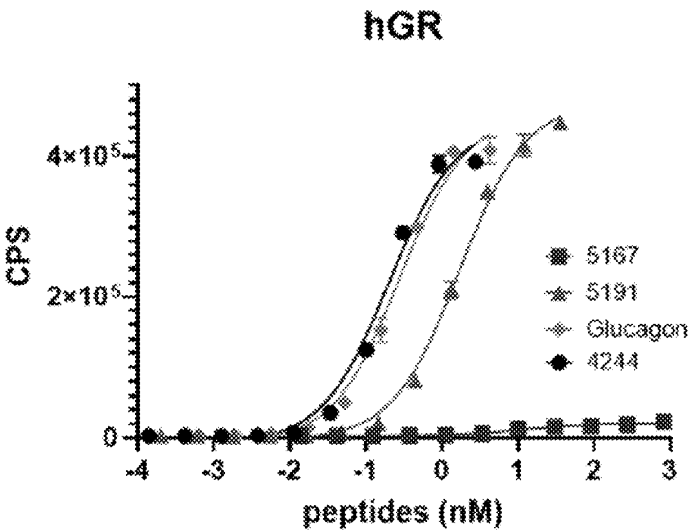


Fig. 39A

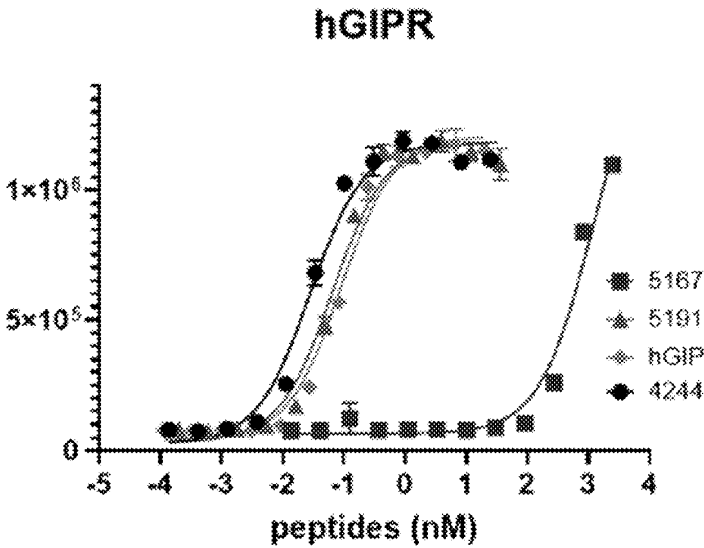


Fig. 39B

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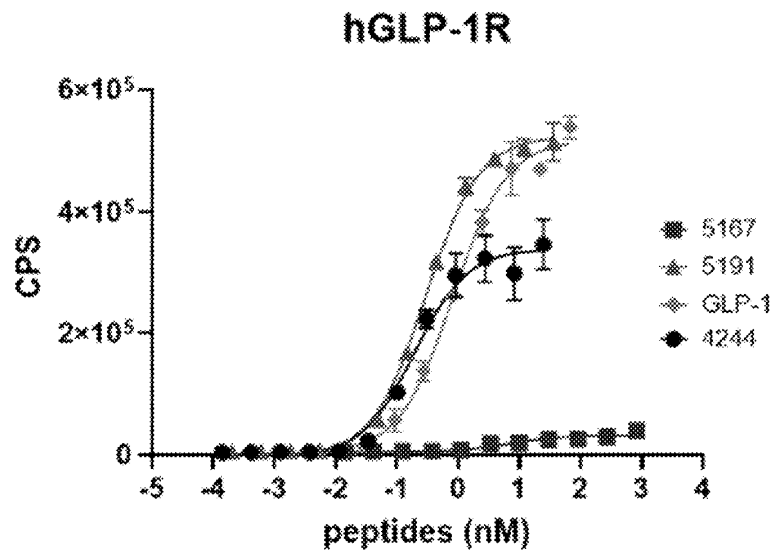


Fig. 39C

60/99

5167 O-**X**CNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**9**ST-NVGSN-T**Z**-NH₂
 5191 O-**X**CNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**6**ST-NVGSN-T**Z**-NH₂
 5129 O-**X**CNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL**Z**ST-NVGSN-T**Z**-NH₂
 4244 Y**J**QGTFTSDYSI**B**LDK**8**AQ**J**AFIEYLLLEGGPSSGAPPPS-NH₂

O = (γE-COC18H32CO₂H)

X = beta-lysine

Z = L, 4-HYP (Trans)

9 = Ac-Orn with O-X-Amylin (2-27) (Peg8) acylated through delta amine

6 = Retatrutide-Peg8 (no lipid) acylated to alpha amine of Orn, and O-X-Amylin (2-27) (Peg8) acylated to delta amine

J = Aib

B = alpha, methyl Leu

8 = K(miniPEG-γE-COC18H36CO₂H)

Fig. 39D

	5167	5191	4244	Standard
hGR	-	1.689	0.201	0.275
hGIPR	1149	0.065	0.028	0.089
hGLP-1R	-	0.295	0.191	0.823

Fig. 39E

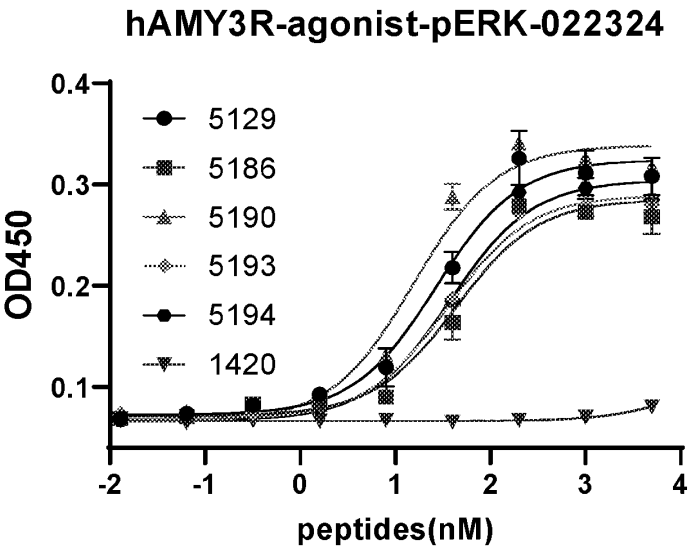


Fig. 40A

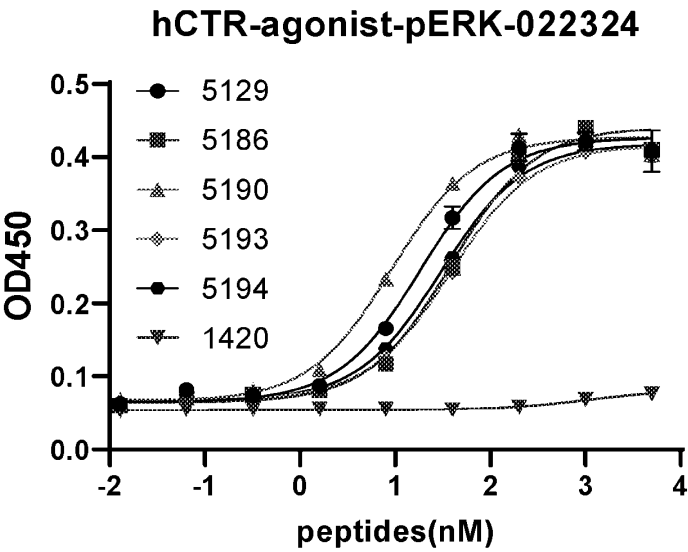


Fig. 40B

5129

O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2

5186

O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL7ST-NVGSN-TZ-NH2

5190

O-XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2

5193

O-XCNTA-TCATQ-RLAEF-LRHSS-----6ST-NVGSN-TZ-NH2

5194

O-XCNTA-TCATQ-RLAEF-LRHSS-----8ST-NVGSN-TZ-NH2

1420

HBEGT-FTSDV-SSYLE-GQAAU-EFIA-WLVRG-RG-OH

O = (VE-COC18H32CO2H)

X = beta-lysine

J = PEG8-L, 4-HYP (Trans)

Z = L, 4-HYP (Trans)

6 = Semaglutide-Peg8,Peg8 (no lipid) acylated to alpha amine of Lys, and O-X-Amylin (2-20, Peg8) acylated to epsilon amine

7 = Semaglutide-Peg8 (no lipid) acylated to the alpha amine of Orn, and O-X-Amylin (2-27, Peg8) acylated to delta amine

8 = Semaglutide-Peg8,Peg8 (no lipid) acylated to epsilon amine of Lys, and O-X-Amylin (2-20, Peg8) acylated to alpha amine

B = Aib

U = mPeg, mPeg, rE(C18 diacid)

Fig. 40C

Ligands	5129	5186	5190	5193	5194	1420
EC50(hAMY3R)	26.75	43.21	15.58	35.63	37.77	-
%	100	61.9	171.7	75.1	70.8	-
EC50(hCTR)	18.46	38.48	9.19	37.92	30.07	-
%	100	48	200.9	48.7	61.4	-

Fig. 40D

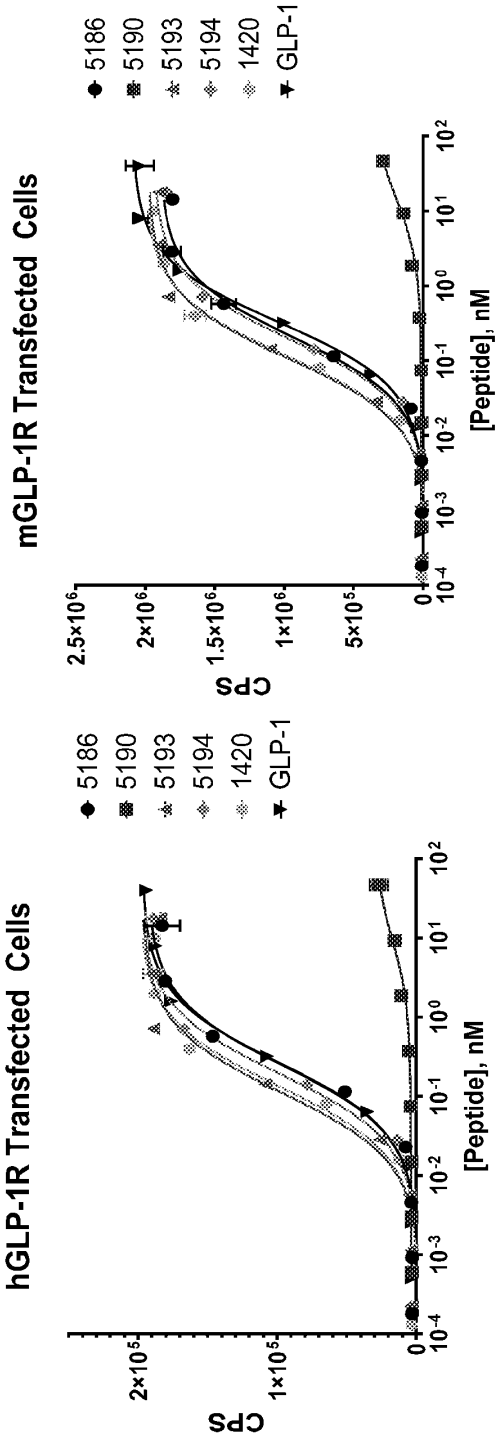


Fig. 41A

Fig. 41B

5186 O-XCNTA-TCATQ-RLAEFF-LRHSS-NNFGA-IL7ST-NVGSN-TZ-NH2
5190 O-XCNTA-TCATQ-RLAEFF-LRHSS-----JST-NVGSN-TZ-NH2
5193 O-XCNTA-TCATQ-RLAEFF-LRHSS-----6ST-NVGSN-TZ-NH2
5194 O-XCNTA-TCATQ-RLAEFF-LRHSS-----8ST-NVGSN-TZ-NH2
1420 HBEGT-FTSDV-SSYLE-GQAAU-EFIA-WLVRG-RG-OH

- O = (γE-COC18H32CO2H)
X = beta-lysine
J = PEG8-L, 4-HYP (Trans)
Z = L, 4-HYP (Trans)
6 = Semaglutide-Peg8,Peg8 (no lipid) acylated to alpha amine of Lys, and
O-X-Amylin (2-20, Peg8) acylated to epsilon amine
7 = Semaglutide-Peg8 (no lipid) acylated to the alpha amine of Orn, and O-
X-Amylin (2-27, Peg8) acylated to delta amine
8 = Semaglutide-Peg8,Peg8 (no lipid) acylated to epsilon amine of Lys, and
O-X-Amylin (2-20, Peg8) acylated to alpha amine
B = Aib
U = mPeg, mPeg, rE(C18 diacid)

Fig. 41C

	5186	5190	5193	5194	1420	Standard
hGLP-1R	0.246	-	0.112	0.194	0.135	0.264
mGLP-1R	0.204	-	0.107	0.191	0.112	0.328

Fig. 41D

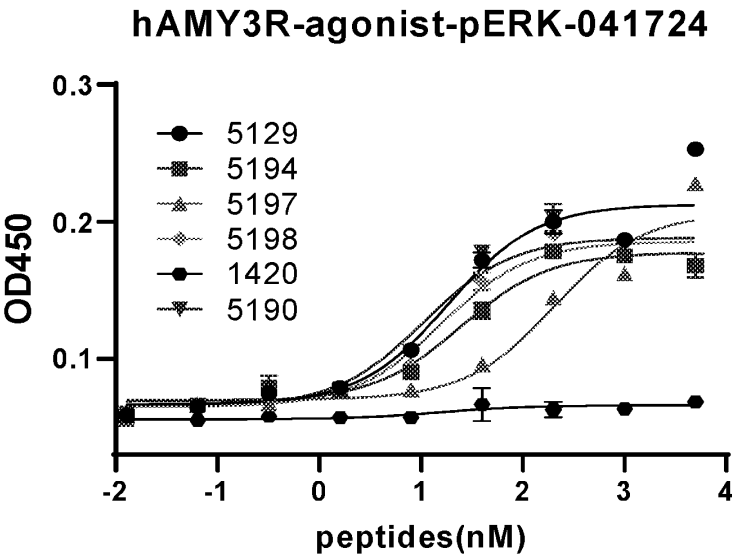


Fig. 42A

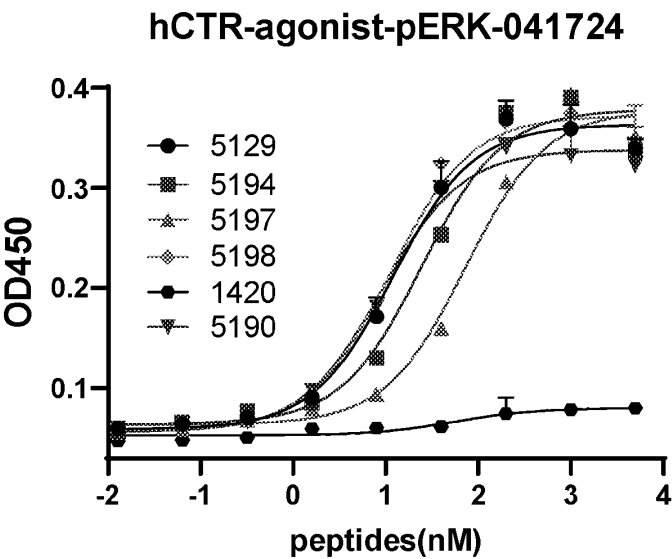


Fig. 42B

5129 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2
5190 O-XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2
5194 O-XCNTA-TCATQ-RLAEF-LRHSS-----8ST-NVGSN-TZ-NH2
5197 O-XCNTA-TCATQ-RLAEF-LRHSS-----7ST-NVGSN-TZ-NH2
5198 O-XCNTA-TCATQ-RLAEF-LRHSS-----6ST-NVGSN-TZ-NH2
1420 HBEGT-FTSDV-SSYLE-GQAAU-EFIA-WLVRG-RG-OH

O = (vE-COC18H32CO2H)

X = beta-lysine

J = PEG8-HYP

Z = L, 4-HYP (Trans)

8 = Semaglutide-Peg8,Peg8 (no lipid) acylated to epsilon amine of Lys, and
O-X-Amylin (2-20, Peg8) acylated to alpha amine

7 = Semaglutide-Peg8,Peg8 (lipid) acylated to epsilon amine of Lys, and O-
X-Amylin (2-20, Peg8) acylated to alpha amine

6 = Semaglutide,des-His1,Ala22-Peg8,Peg8 (no lipid) acylated to epsilon
amine of Lys, and O-X-Amylin (2-20, Peg8) acylated to alpha amine

B = Aib

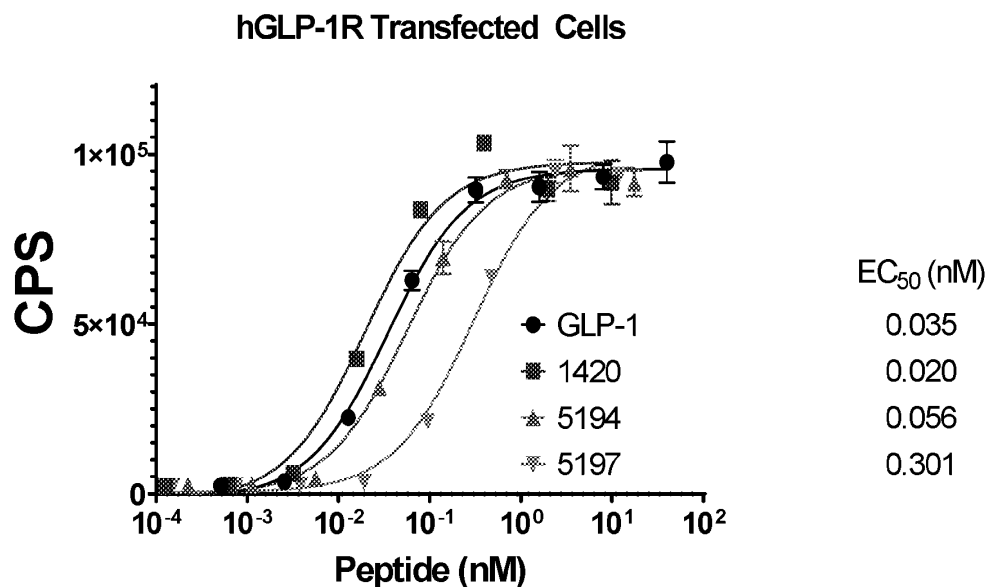
U = mPeg, mPeg, rE(C18 diacid)

Fig. 42C

Ligands	5129	5194	5197	5198	1420	5190
EC50						
(hAMY3R)	18.31	24.48	206.7	15.78	-	10.63
%	100	74.8	88.6	116	-	172.2
EC50 (hCTR)	11.98	24.49	73.13	11.26	-	9.054
%	100	48.9	16.4	106.4	-	132

Fig. 42D

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5194 O-XCNTA-TCATQ-RLAEF-LRHSS-----8ST-NVGSN-TZ-NH₂

5197 O-XCNTA-TCATQ-RLAEF-LRHSS-----7ST-NVGSN-TZ-NH₂

1420 HBEGT-FTSDV-SSYLE-GQAAU-EFIA-WLVRG-RG-OH

O = (γE-COC18H32CO₂H)

X = beta-lysine

Z = L, 4-HYP (Trans)

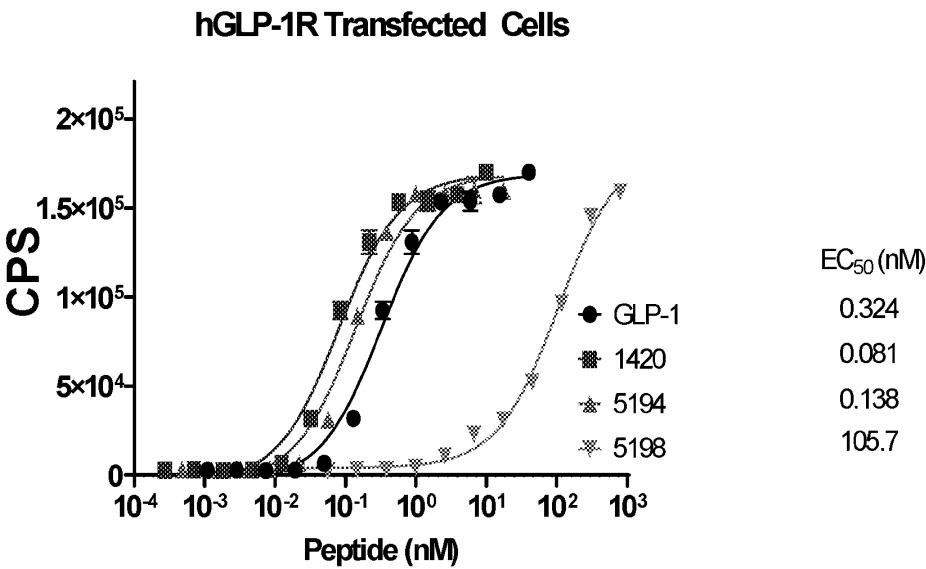
8 = Semaglutide-Peg8, Peg8 (no lipid) acylated to epsilon amine of Lys, and O-X-Amylin (2-20, Peg8) acylated to alpha amine

7 = Semaglutide-Peg8, Peg8 (lipid) acylated to epsilon amine of Lys, and O-X-Amylin (2-20, Peg8) acylated to alpha amine

B = Aib

U = mPeg, mPeg, rE(C18 diacid)

Fig. 43



5194 O-XCNTA-TCATQ-RLAEF-LRHSS-----8ST-NVGSN-TZ-NH2

5198 O-XCNTA-TCATQ-RLAEF-LRHSS-----6ST-NVGSN-TZ-NH2

1420 HBEGT-FTSDV-SSYLE-GQAAU-EFIA-WLVRG-RG-OH

O = (γE-COC18H32CO2H)

X = beta-lysine

Z = L, 4-HYP (Trans)

8 = Semaglutide-Peg8,Peg8 (no lipid) acylated to epsilon amine of Lys, and O-X-Amylin (2-20, Peg8) acylated to alpha amine

6 = Semaglutide,des-His1,Ala22-Peg8,Peg8 (no lipid) acylated to epsilon amine of Lys, and O-X-Amylin (2-20, Peg8) acylated to alpha amine

B = Aib

U = mPeg, mPeg, rE(C18 diacid)

Fig. 44

hAMY3R-agonist-pERK-053124

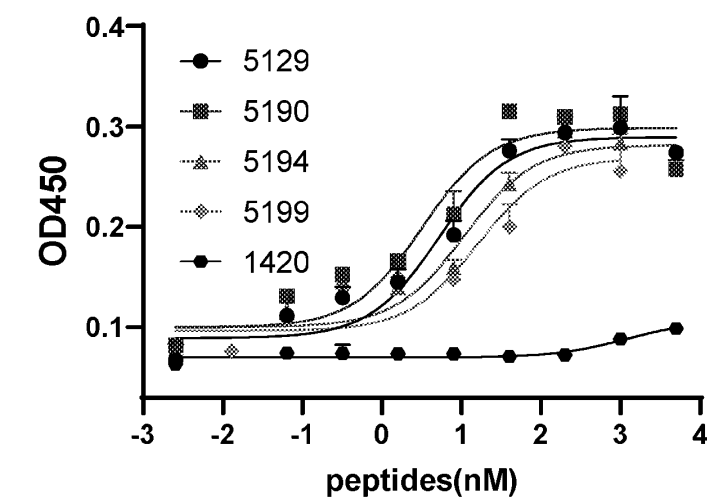


Fig. 45A

hCTR-agonist-pERK-053124

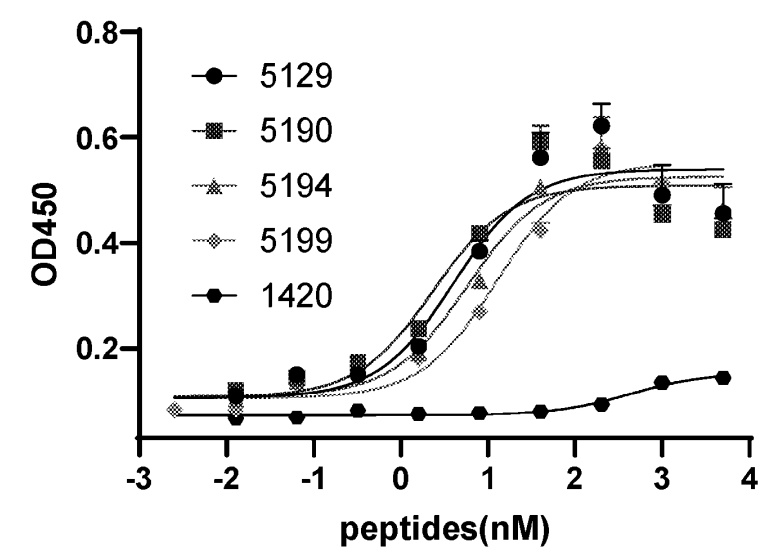


Fig. 45B

5129 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-ILZST-NVGSN-TZ-NH2
5190 O-XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2
5194 O-XCNTA-TCATQ-RLAEF-LRHSS-----8ST-NVGSN-TZ-NH2
5199 O-XCNTA-TCATQ-RLAEF-LRHSS-----6ST-NVGSN-TZ-NH2
1420 HBEGT-FTSDV-SSYLE-GQAAU-EFIA-WLVRG-RG-OH

Fig. 45C

- O = (γE-COC18H32CO2H)
- X = beta-lysine
- J = PEG8-L, 4-HYP (Trans)
- Z = L, 4-HYP (Trans)
- 8 = Semaglutide-Peg8,Peg8 (no lipid) acylated to epsilon amine of Lys, and O-X-Amylin (2-20, Peg8) acylated to alpha amine
- 6 = Tirzepatide,-Peg8 (no lipid) acylated to epsilon amine of Lys, and O-X-Amylin (2-20, Peg8) acylated to alpha amine
- B = Aib
- U = mPeg, mPeg, rE(C18 diacid)

Ligands	5129	5190	5194	5199	1420
EC50(hAMY3R)	5.223	3.195	10.8	15.99	-
%	100	163.5	48.4	32.7	-
EC50(hCTR)	3.989	2.316	5.75	12.81	-
%	100	172.2	69.4	31.1	-

Fig. 45D

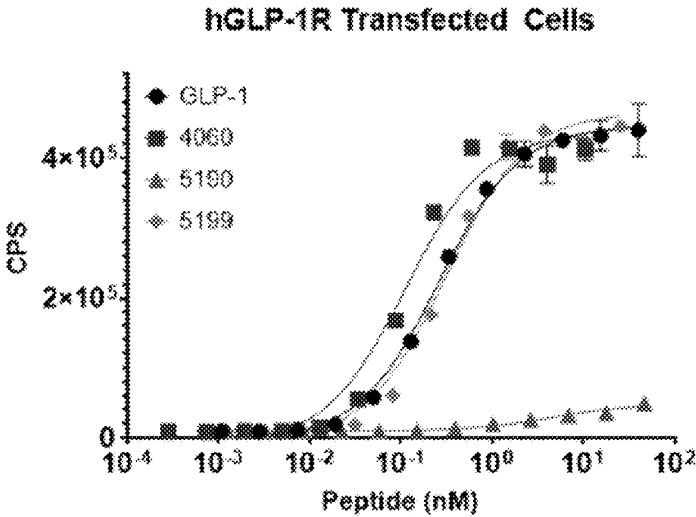


Fig. 46A

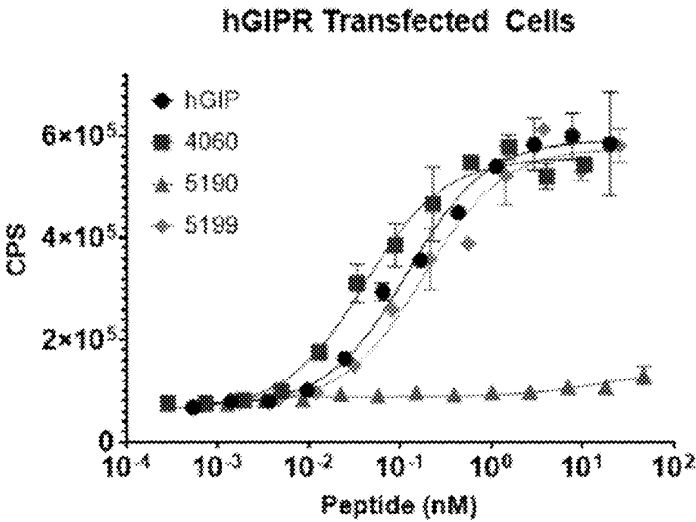


Fig. 46B

5190 O-**X**CNTA-TCATQ-RLAEF-LRHSS-----**J**ST-NVGSN-T**Z**-NH2
5199 O-**X**CNTA-TCATQ-RLAEF-LRHSS-----**6**ST-NVGSN-T**Z**-NH2
4060 Y**B**EGT FTS DY S**I**BLD KIA**Q**U AFVQW LIAGG PSSGA PPFS-NH2

Fig. 46C

O = (γE-COC18H32CO2H)
X = beta-lysine
J = PEG8-L, 4-HYP (Trans)
Z = L, 4-HYP (Trans)
6 = Tirzepatide-Peg8 (no lipid) acylated to epsilon amine of Lys, and
O-X-Amylin (2-20, Peg8) acylated to alpha amine
B = Aib
U = mPeg,mPeg,rE(C20 diacid)

	4060	5190	5199	Standard
hGLP-1R	0.113	-	0.308	0.259
hGIP	0.041	-	0.183	0.121

Fig. 46D

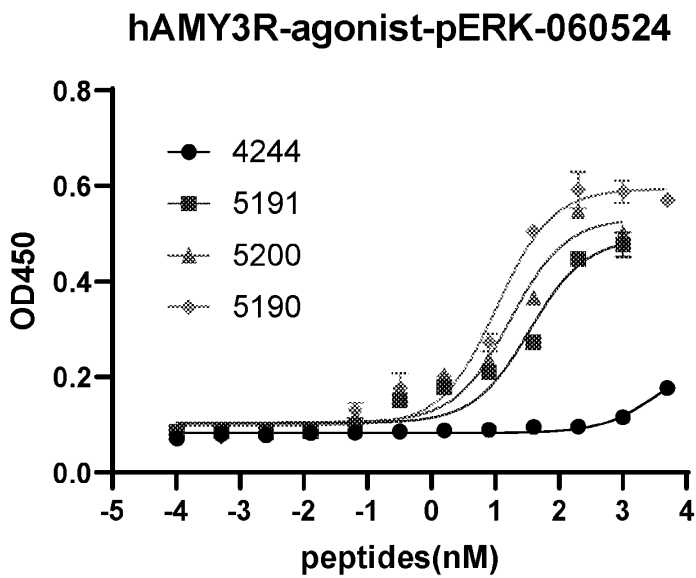


Fig. 47A

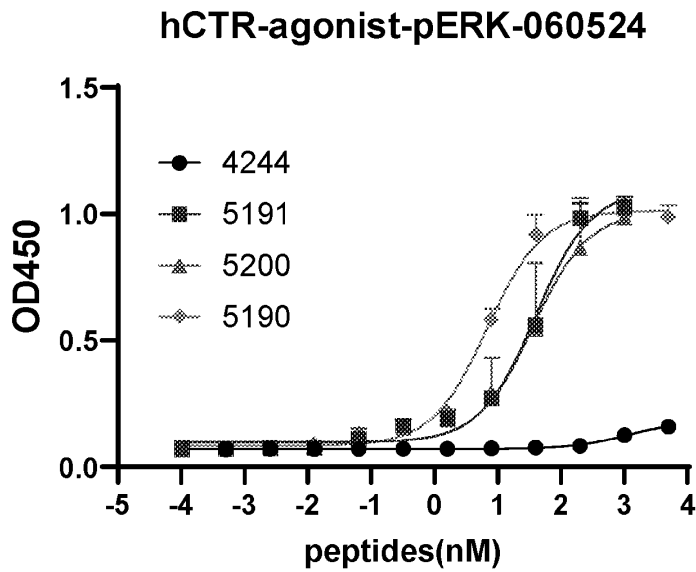


Fig. 47B

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5190 O-XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2
5191 O-XCNTA-TCATQ-RLAEF-LRHSS-NNFGA-IL6ST-NVGSN-TZ-NH2
5200 O-XCNTA-TCATQ-RLAEF-LRHSS-----8ST-NVGSN-TZ-NH2
4244 YXQGT FTSDY SIBLD KUAQX AFIEY LLEGG PSSGA PPPS-NH2

O = (γE-COC18H32CO2H)
X = beta-lysine
J = PEG8-L, 4-HYP (Trans)
Z = L, 4-HYP (Trans)
6 = Retatrutide-Peg8 (no lipid) acylated to alpha amine of Orn, and O-X-Amylin (2-27, Peg8) acylated to delta amine
8 = Retatrutide-Peg8 (no lipid) acylated to epsilon amine of Lys, and O-X-Amylin (2-20, Peg8) acylated to alpha amine
B = alpha, methyl Leu

Fig. 47C

Ligands	4244	5191	5200	5190
EC50 (hAMY3R)	–	34.5	17.15	10.58
%	–	30.7	61.7	100
EC50 (hCTR)	–	39.56	36.15	6.837
%	–	17.3	18.9	100

Fig. 47D

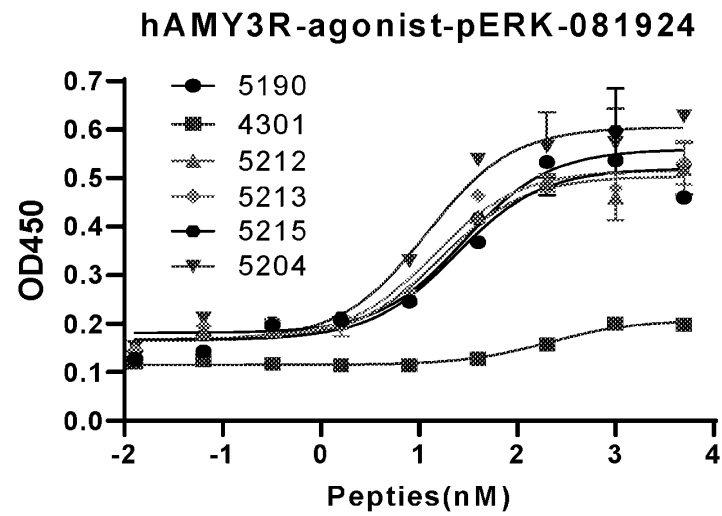


Fig. 48A

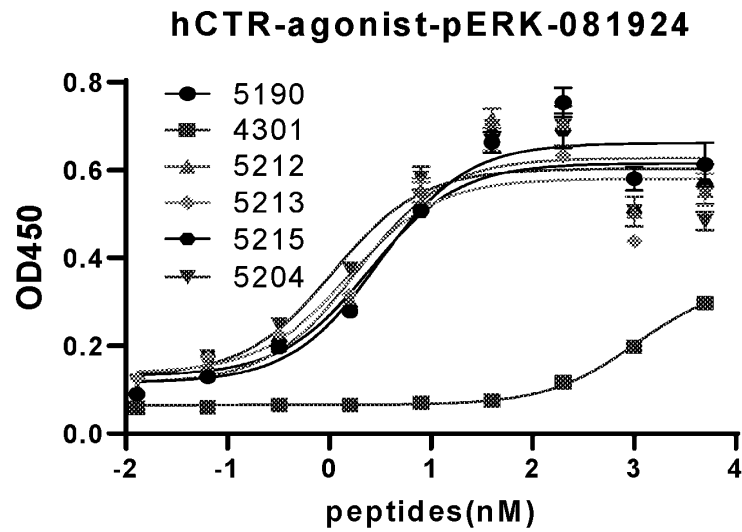


Fig. 48B

5190 O-XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2
5204 O-XCNTA-TCATQ-RLAEF-LRHSS-----2ST-NVGSN-TZ-NH2
5212 O-XCNTA-TCATQ-RLAEF-LRHSS-----3ST-NVGSN-TZ-NH2
5213 O-XCNTA-TCATQ-RLAEF-LRHSS-----4ST-NVGSN-TZ-NH2
5215 O-XCNTA-TCATQ-RLAEF-LRHSS-----5ST-NVGSN-TZ-NH2
4301 Y9QGT FTSDY SIBLD KUAQ9 AFVQW LLEGG PSSGA PPPS-NH2

O = (γE-COC18H32CO2H)
X = beta-lysine
J = PEG8-L, 4-HYP (Trans)
Z = L, 4-Hyp (Trans)
2 = Peg8-Lys(Azido)
3 = Peg8-Lys(Triazole) to C-terminus of Retatrutide, desY1, A22-Peg8 (no lipid)
4 = Peg8-Lys(Triazole) to C-terminus of Retatrutide-Peg8 (no lipid)
5 = Peg8-Lys(Triazole) to C-terminus of 4301-Peg8 (no lipid)
9 = AIB
B = alpha, methyl Leu
U = mPeg,mPeg,rE(C20 diacid)

Fig. 48C

Ligands	5190	4301	5212	5213	5125	5204
EC50(hAMY3R)	23.84	-	16.45	14.11	28.52	11.93
%	100	-	144.9	169	83.6	199.8
EC50(hCTR)	3.056	-	1.895	1.556	2.515	1.088
%	100	-	161.2	196.4	121.5	280.9

Fig. 48D

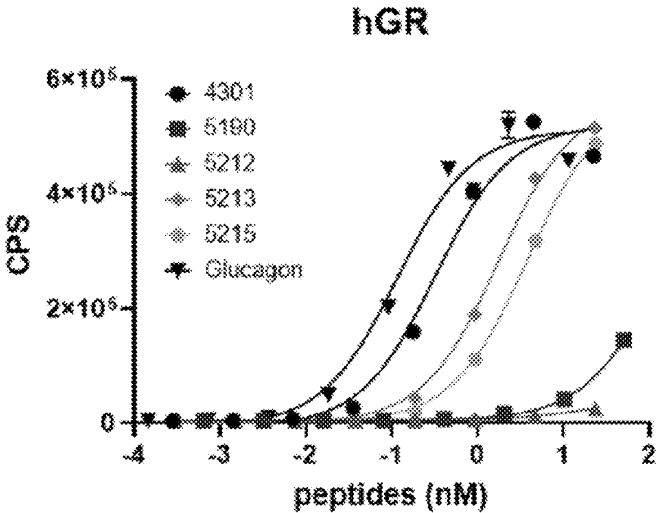


Fig. 49A

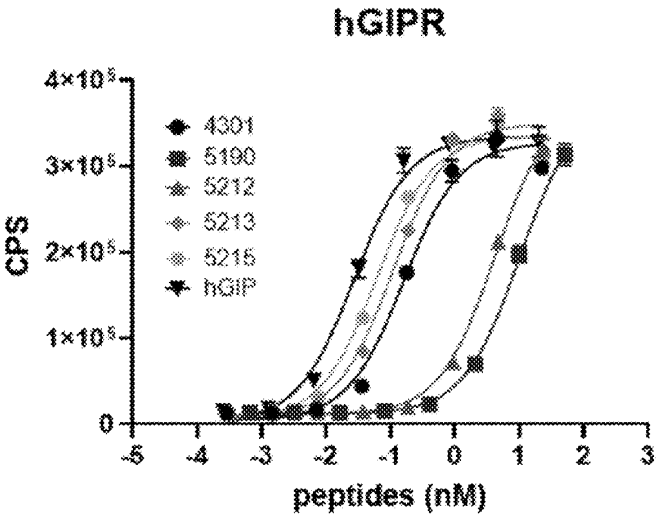


Fig. 49B

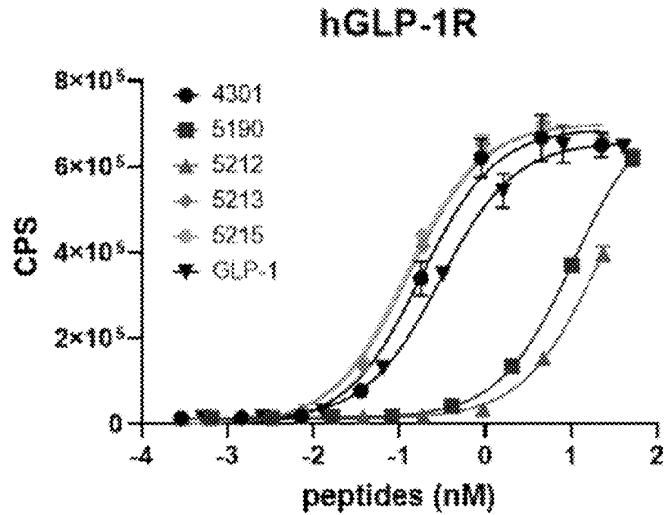


Fig. 49C

5190 O-XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2
5212 O-XCNTA-TCATQ-RLAEF-LRHSS-----3ST-NVGSN-TZ-NH2
5213 O-XCNTA-TCATQ-RLAEF-LRHSS-----4ST-NVGSN-TZ-NH2
5215 O-XCNTA-TCATQ-RLAEF-LRHSS-----5ST-NVGSN-TZ-NH2
4301 Y9QGT FTS DY SIBLD KUAQ9 AFVQW LLEGG PSSGA FPPS-NH2

O = (γE-COC18H32CO2H)

X = beta-lysine

J = PEG8-L, 4-HYP (Trans)

Z = L, 4-Hyp (Trans)

3 = Peg8-Lys(Triazole) to C-terminus of Retatrutide, desY1, A22-Peg8 (no lipid)

4 = Peg8-Lys(Triazole) to C-terminus of Retatrutide-Peg8 (no lipid)

5 = Peg8-Lys(Triazole) to C-terminus of 4301-Peg8 (no lipid)

9 = AIB

B = alpha, methyl Leu

U = mPeg,mPeg,rE(C20 diacid)

Fig. 49D

	4301	5190	5212	5213	5215	Standard
hGR	0.321	-	16.25	1.733	3.780	0.116
hGIPR	0.159	9.928	4.135	0.109	0.061	0.027
hGLP-1R	0.177	10.57	19.26	0.129	0.117	0.295

Fig. 49E

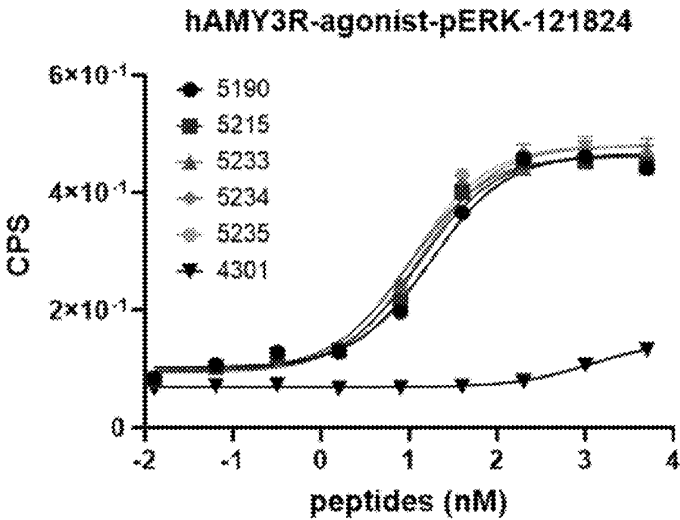


Fig. 50A

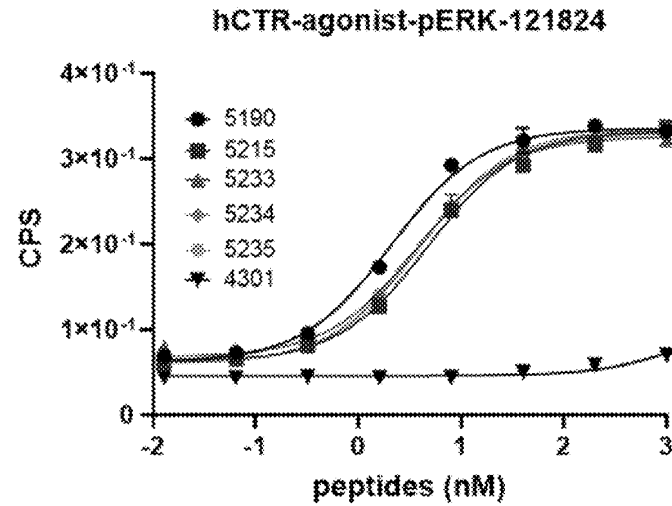


Fig. 50B

4301 Y9QGT FTSDY SIBLD KUAQ9 AFVQW LLEGG PSSGA PPPS-NH2
5215 O-XCNTA-TCATQ-RLAEF-LRHSS-----5ST-NVGSN-TZ-NH2
5233 O-XCNTA-TCATQ-RLAEF-LRHSS-----6ST-NVGSN-TZ-NH2
5234 O-XCNTA-TCATQ-RLAEF-LRHSS-----7ST-NVGSN-TZ-NH2
5235 O-XCNTA-TCATQ-RLAEF-LRHSS-----8ST-NVGSN-TZ-NH2

9 = AIB

B = alpha, methyl Leu

U = mPeg,mPeg,rE(C20 diacid)

O = (γE-COC18H32CO2H)

X = beta-lysine

Z = L, 4-Hyp (Trans)

5 = PEG8-Lys(Triazole) to C-terminus of 4301-Peg8 (no lipid)

6 = PEG8-Lys(Thioether) to C-terminus of 4301-Peg8 (no lipid)

7 = PEG8-Lys(Disulfide) to C-terminus of 4301-Peg8 (no lipid)

8 = PEG8-Lys(Penicillamine Disulfide) to C-terminus of 4301-Peg8 (no lipid)

Fig. 50C

	5190	5215	5233	5234	5235	4301
hAMY3R	17.68	12.79	10.15	12.89	10.63	-
hCTR	2.088	4.734	3.751	3.986	3.740	-

Fig. 50D

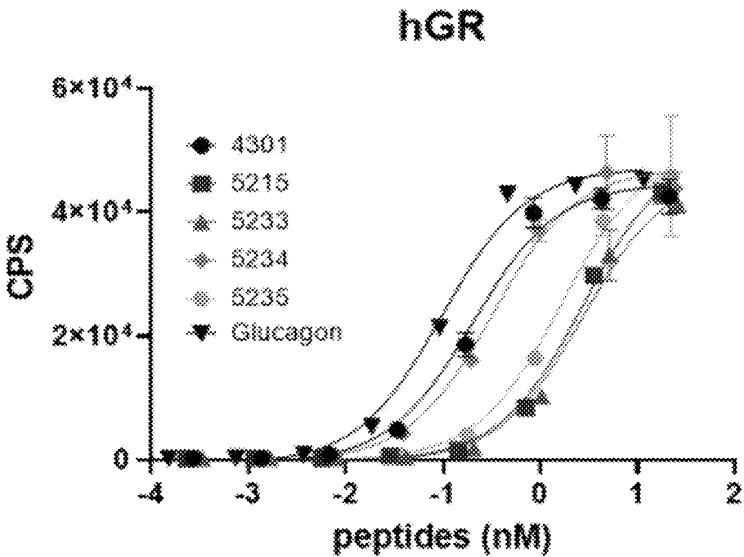


Fig. 51A

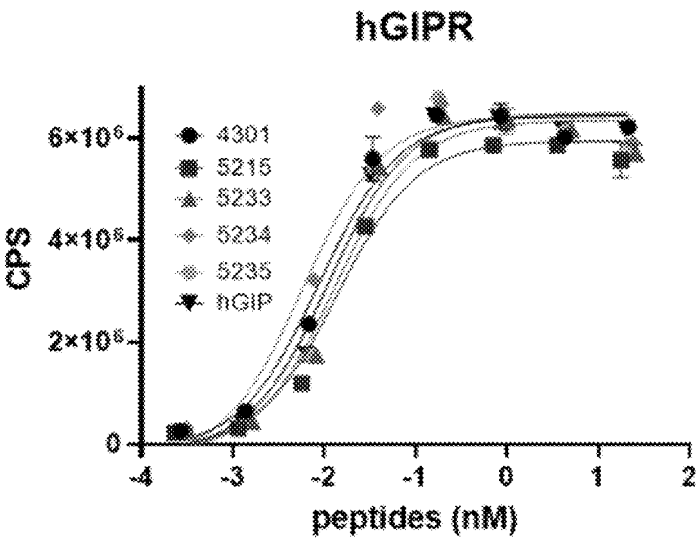


Fig. 51B

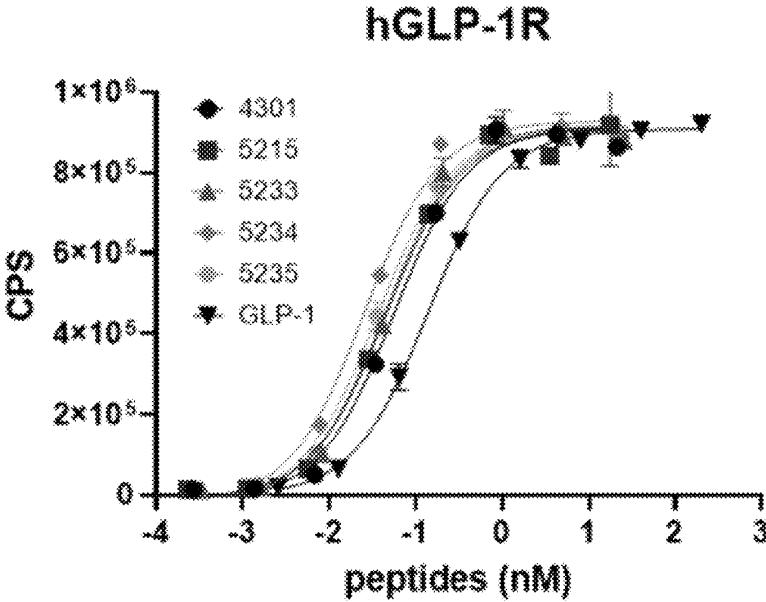


Fig. 51C

Y**9**QGT FTS DY SIBLD KUAQ**9** AFVQW LLEGG PSSGA PPPS-NH2
O-XCNTA-TCATQ-RLAEF-LRHSS-----**5**ST-NVGSN-T**Z**-NH2
O-XCNTA-TCATQ-RLAEF-LRHSS-----**6**ST-NVGSN-T**Z**-NH2
O-XCNTA-TCATQ-RLAEF-LRHSS-----**7**ST-NVGSN-T**Z**-NH2
O-XCNTA-TCATQ-RLAEF-LRHSS-----**8**ST-NVGSN-T**Z**-NH2

9 = AIB

B = alpha, methyl Leu

U = mPeg,mPeg,rE(C20 diacid)

O = (γE-COC18H32CO2H)

X = beta-lysine

Z = L, 4-Hyp (Trans)

5 = PEG8-Lys(Triazole) to C-terminus of 4301-Peg8 (no lipid)

6 = PEG8-Lys(Thioether) to C-terminus of 4301-Peg8 (no lipid)

7 = PEG8-Lys(Disulfide) to C-terminus of 4301-Peg8 (no lipid)

8 = PEG8-Lys(Penicillamine Disulfide) to C-terminus of 4301-Peg8 (no lipid)

Fig. 51D

	4301	5215	5233	5234	5235	Standard
hGR	0.200	2.763	2.753	0.318	1.625	0.096
hGIPR	0.009	0.014	0.013	0.006	0.011	0.011
hGLP-1R	0.056	0.046	0.044	0.026	0.037	0.139

Fig. 51E

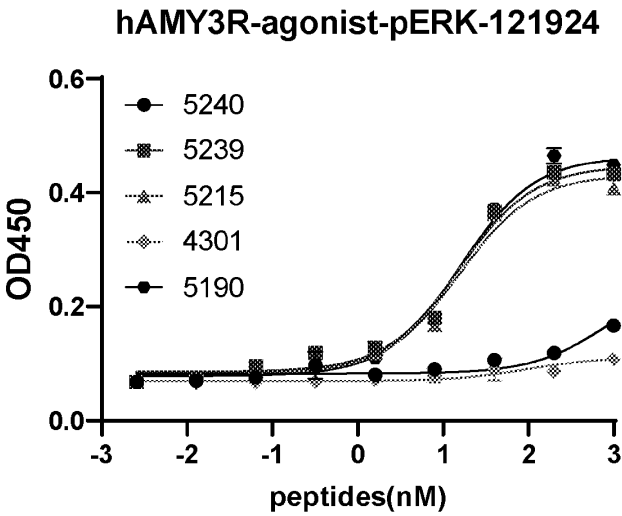


Fig. 52A

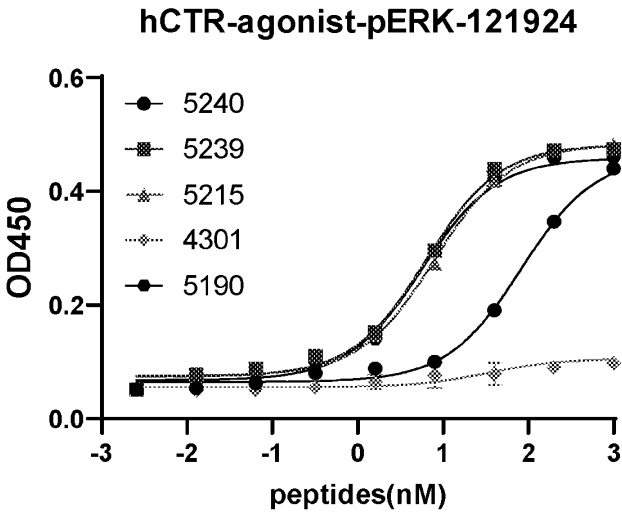


Fig. 52B

4301 Y9QGT FTS DY SIBLD KUAQ9 AFVQW LLEGG PSSGA PPPS-NH2
5190 O-XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2
5215 O-XCNTA-TCATQ-RLAEF-LRHSS-----5ST-NVGSN-TZ-NH2
5239 O-XCNTA-TCATQ-RLAEF-LRHSS-----6ST-NVGSN-TZ-NH2
5240 O-XCNTA-TCATQ-RLAEF-LRHSS-----5ST-NVGSN-TY-COOH

9 = AIB

B = alpha, methyl Leu

U = mPeg,mPeg,rE(C20 diacid)

O = (γE-COC18H32CO2H)

X = beta-lysine

J = PEG8-L, 4-HYP (Trans)

Z = L, 4-Hyp (Trans)

5 = PEG8-Lys(Triazole) to C-terminus of 4301-Peg8 (no lipid)

6 = PEG8-Lys(Triazole) to C-terminus of 4301 (desY1, A22)-Peg8 (no lipid)

Fig. 52C

	5190	4301	5215	5239	5240
hAMY3R	15.91	-	15.50	15.55	-
hCTR	5.648	-	7.855	6.291	82.45

Fig. 52D

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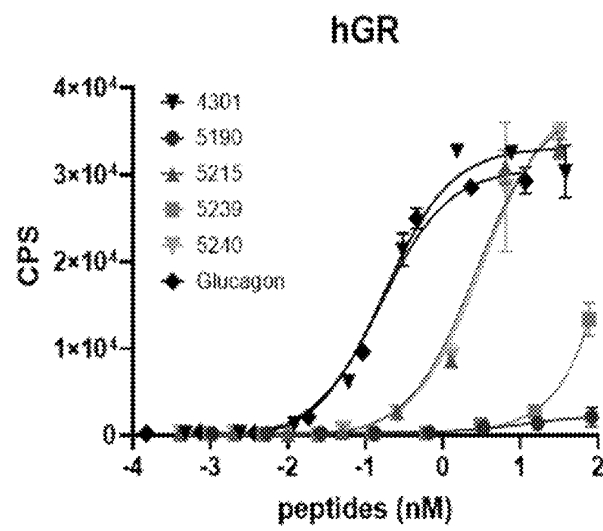


Fig. 53A

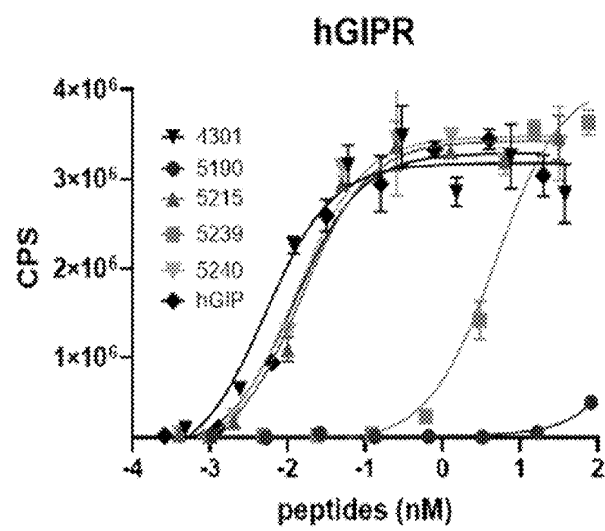


Fig. 53B

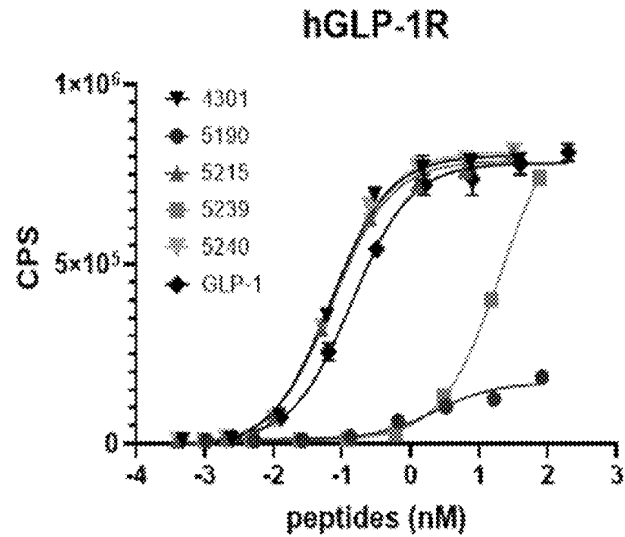


Fig. 53C

4301	Y9QGT FTS DY SIBLD KUAQ9 AFVQW LLEGG PSSGA PPPS-NH2
5190	O-XCNTA-TCATQ-RLAEF-LRHSS-----JST-NVGSN-TZ-NH2
5215	O-XCNTA-TCATQ-RLAEF-LRHSS-----5ST-NVGSN-TZ-NH2
5239	O-XCNTA-TCATQ-RLAEF-LRHSS-----6ST-NVGSN-TZ-NH2
5240	O-XCNTA-TCATQ-RLAEF-LRHSS-----5ST-NVGSN-TY-COOH

9 = AIB

B = alpha, methyl Leu

U = mPeg,mPeg,rE(C20 diacid)

O = (γE-COC18H32CO2H)

X = beta-lysine

J = PEG8-L, 4-HYP (Trans)

Z = L, 4-Hyp (Trans)

5 = PEG8-Lys(Triazole) to C-terminus of 4301-Peg8 (no lipid)

6 = PEG8-Lys(Triazole) to C-terminus of 4301 (desY1, A22)-Peg8 (no lipid)

Fig. 53D

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	4301	5190	5215	5239	5240	Standard
hGR	0.173	-	2.671	-	3.232	0.159
hGIPR	0.005	-	0.015	4.848	0.013	0.012
hGLP-1R	0.068	-	0.072	20.57	0.072	0.139

Fig. 53E

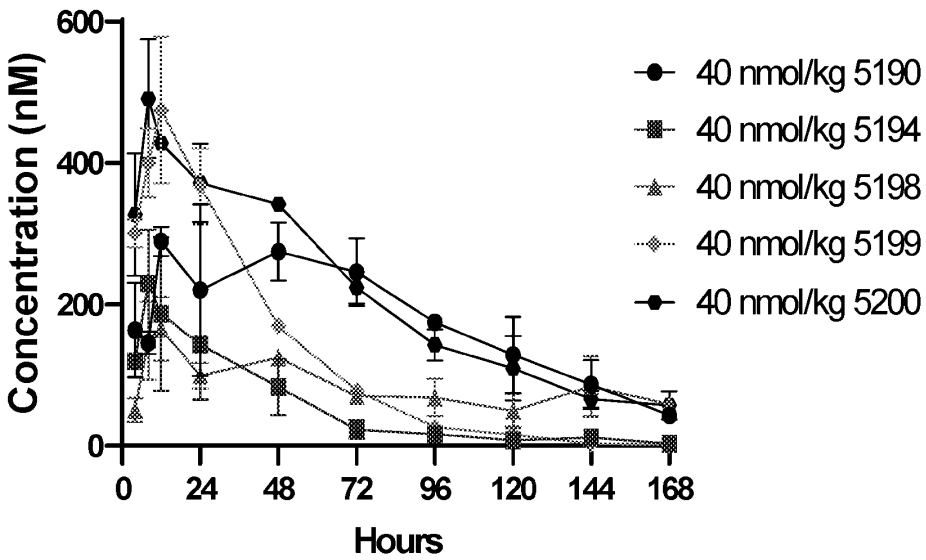


Fig. 54

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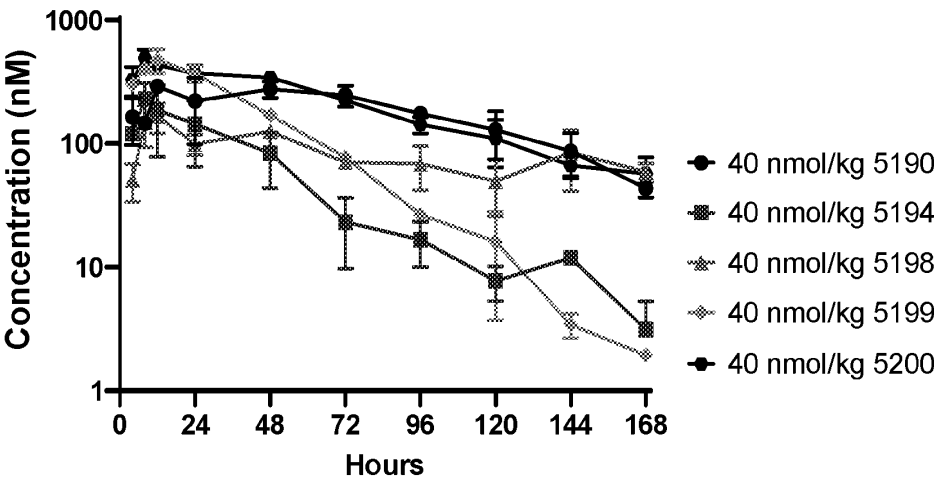


Fig. 55

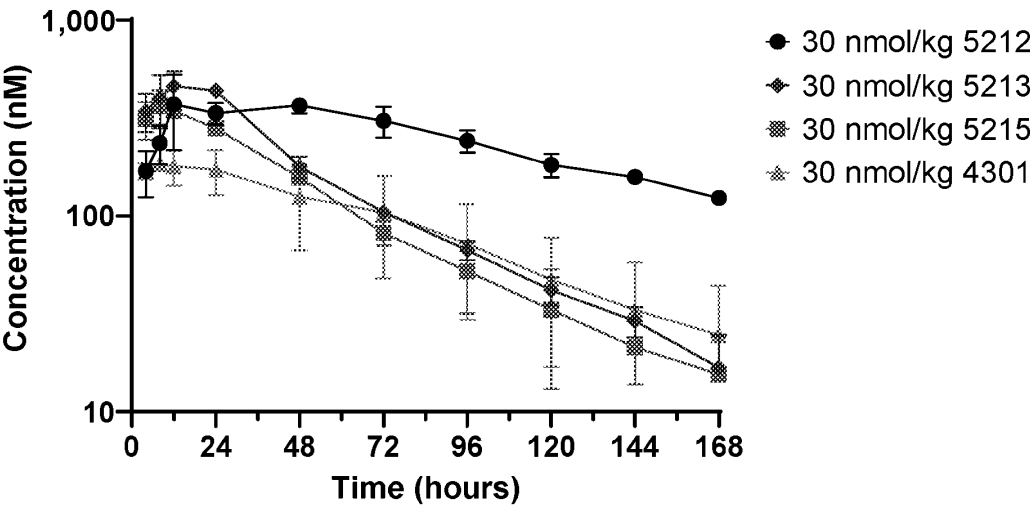


Fig. 56

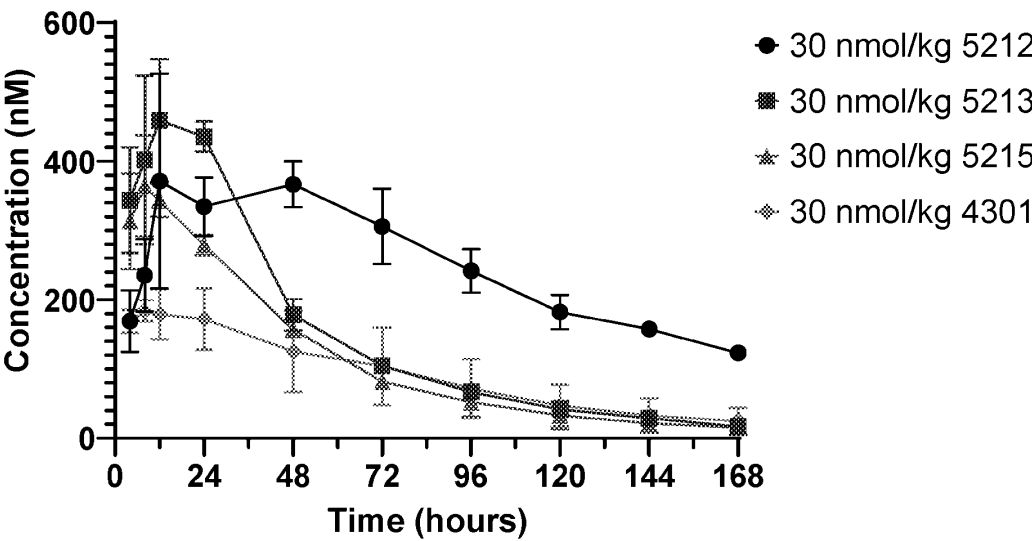


Fig. 57

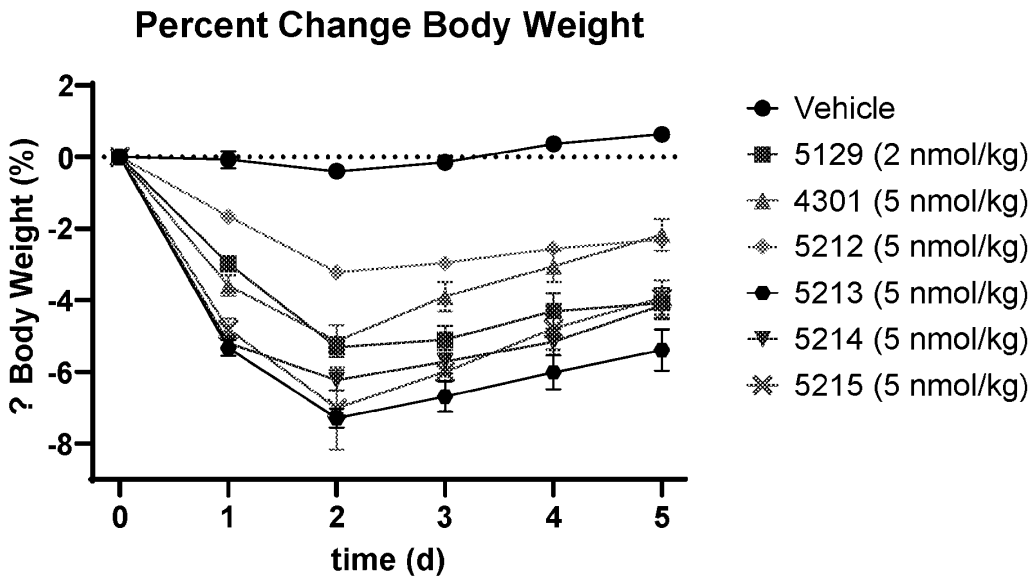


Fig. 58

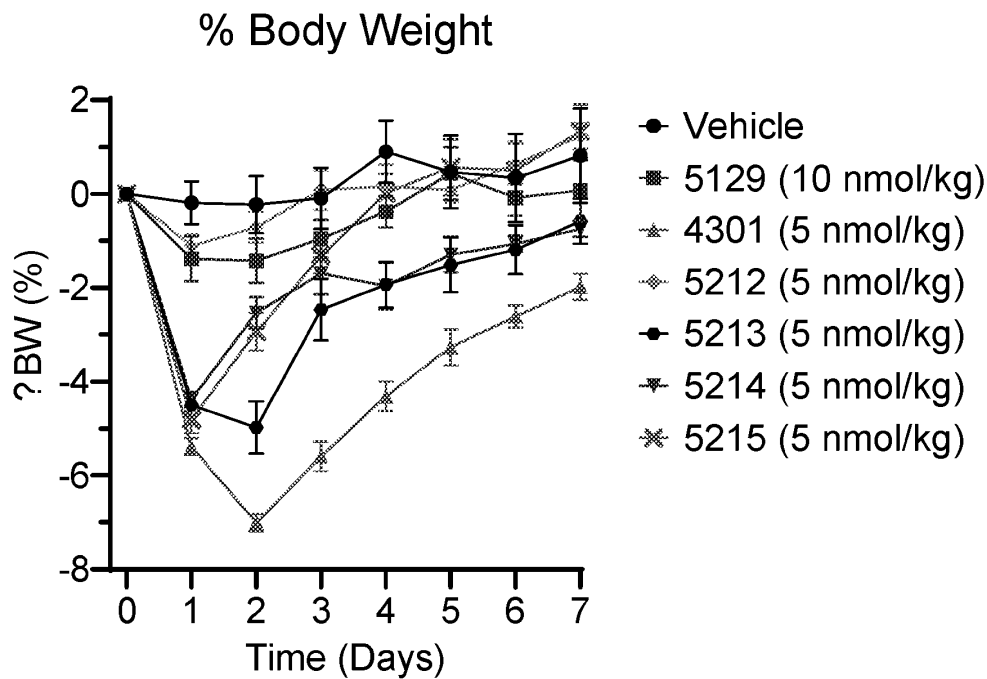


Fig. 59

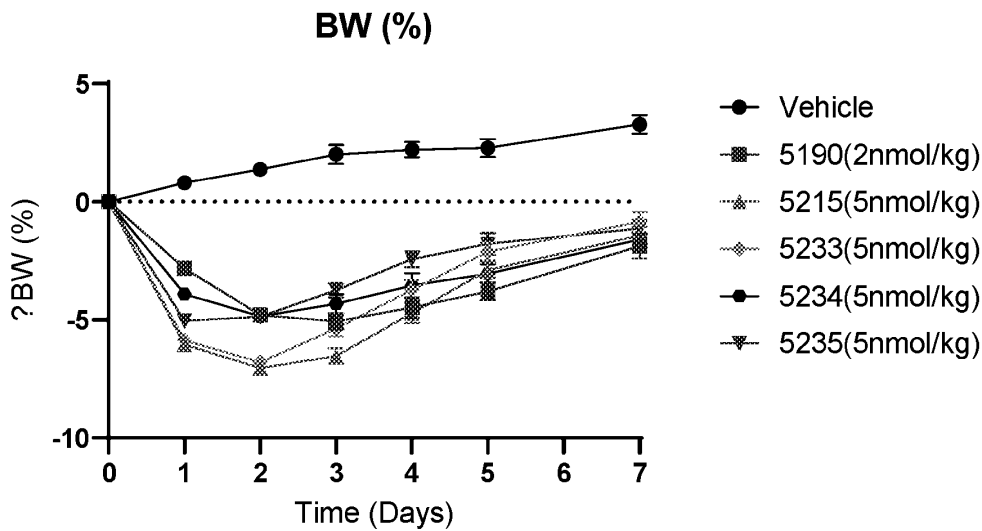


Fig. 60

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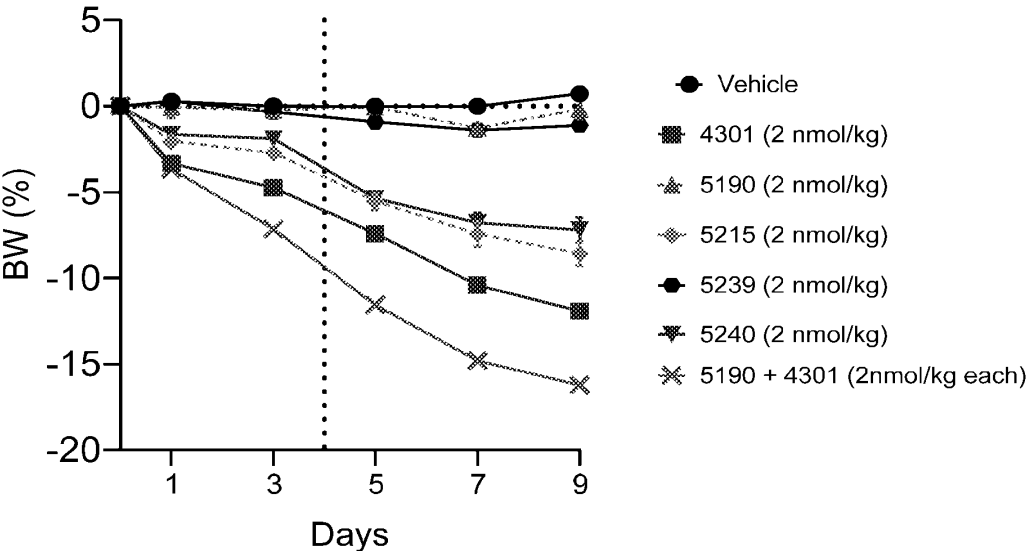


Fig. 61

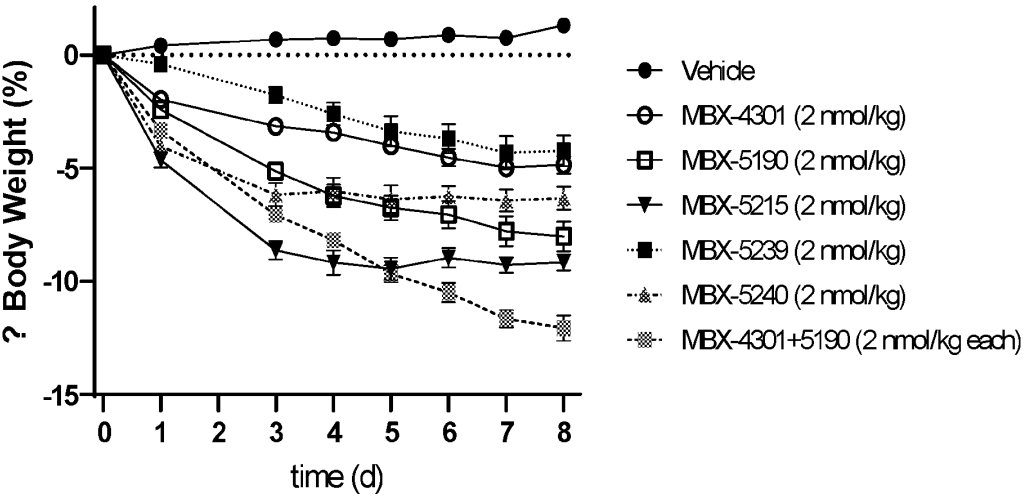


Fig. 62

Fig. 63

Cmp	SEQ ID NO:	Sequence
1420	19	H-Aib-EGTFTSDVSSYLEGQAAK(mPeg-mPeg- γ E-COC16H32COOH)EFLAWLVGRG-acid
4060	20	Y-Aib-EGTFTSDYSI-Aib-LDKIAQK(mPeg-mPeg- γ E-COC18H36CO2H)AFVQWLIAGGPSSGAPPPS-amide
4244	21	Y-Aib-QGTFTSDYSI-aMe-L-LDKK(mPeg- γ E-COC18H36CO2H)AQ-Aib-AFIEYLLEGGPSSGAPPPS-amide
4274	22	Y-Aib-EGT- α Me,F-TSDYSI-Aib-LEKTAAG((miniPEG)2- γ E-COC18H36CO2H)AFVQWLIAGGPSSGAPPPS-amide
4274A	23	Y-Aib-EGT- α Me,F-TSDYSI-Aib-LEKTAAG((miniPEG)2- γ E-COC18H36CO2H)AQ-Aib-AFVQWLIAGGPSSGAPPPS-amide
4301	24	Y-Aib-QGTFTSDYSI-aMe,L-LDKK(mPeg-mPeg- γ E-COC18H36CO2H)AQ-Aib-AFVQWLIAGGPSSGAPPPS-amide
4301A	25	Y-Aib-QGTFTSDYSI-aMe,L-LDKK(mPeg-mPeg- γ E-COC18H36CO2H)AQ-Aib-AFVQWLIAGGPSSGAPPPS-amide
5053	26	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGPILPPTNVGSNTY-amide
5061	27	KCNTATCATQRLANFLVHSSNNFGAILPSTNVGSNTY-amide
5063	28	KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY-amide
5064	29	KCNTATCATQRLANFLVHSSNNFGAIL-Hyp-STNVGSNTY-amide
5071	30	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGPILPPTNVGSNTY-amide
5079	31	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSNTY-amide
5092	32	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGAIL-Hyp-ILSSTNVGSNTY-amide
5093	33	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGAILS-Hyp-INVGSTP-amide
5113	34	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSNTY-amide
5114	35	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSNT-Aze-amide
5115	36	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSNT-Pip-amide
5128	37	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSNTY-amide
5129	38	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSNTY-amide
5130	39	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSNTY-amide
5136	40	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGAIL-Hyp-Hyp-TNVGSNTP-amide
5137	41	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGPIL-Hyp-Hyp-TNVGSNTP-amide
5138	42	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFG-Hyp-IL-Hyp-TNVGSNTP-amide
5139	43	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-Hyp-Hyp-TNVGSNTY-amide
5140	44	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-3Hyp-3Hyp-NVGSTP-amide
5142	45	(COOH)C18H36CO- γ E-KCNTATCATQRLAEFLRHSSNNFGPILPPTNVGSNTY-amide
5143	46	CH3CO-Hyp-((COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL)STNVGSNTY-amide
5144	47	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGPIL-Hyp-Hyp-TNVGSNTY-amide
5145	48	CH3CO-Hyp((COOH)C18H36CO- β K-CNTATCATQRLAEFLRHSSNNFGAILS)TNVGSNTY-amide
5146	49	CH3CO-S((COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSNTY-amide

Fig. 63 (Cont. 1)

5147	SEQ ID NO: 50	CH3CO-T((COOH)C18H36CO- γ E- β K-CNTATCA)QRLAEFLRHSSNNFGAIL-Hyp-STNVGSNT-Hyp-amide
5148	SEQ ID NO: 51	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-acid
5149	SEQ ID NO: 52	CH3CO-Hyp-STNVGSNT-Hyp-amide
5150	SEQ ID NO: 53	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAILS-acid
5151	SEQ ID NO: 54	CH3CO-Hyp-TNVGSNT-Hyp-amide
5152	SEQ ID NO: 55	CH3CO-cis,Hyp-((COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL)STNVGSNT-Hyp-amide
5155	SEQ ID NO: 56	β K-CNTATCATQRLAEFLRHSSNNFGAIL-acid
5157	SEQ ID NO: 57	(COOH)C18H36CO- γ E- β K-CNTSTCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSNT-Hyp-amide
5158	SEQ ID NO: 58	(COOH)C18H36CO- γ E- β K-CNTATCATARLAEFLRHSSNNFGAIL-Hyp-STNVGSNT-Hyp-amide
5159	SEQ ID NO: 59	(COOH)C18H36CO- γ E- β K-CNTSTCATARLAEFLRHSSNNFGAIL-Hyp-STNVGSNT-Hyp-amide
5160	SEQ ID NO: 60	CH3CO-Om((COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL)STNVGSNT-Hyp-amide
5161	SEQ ID NO: 61	β K-CNTATCA-acid
5163	SEQ ID NO: 62	β K-CNTATCATQRLAEFLRH-acid
5164	SEQ ID NO: 63	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-mPeg-Hyp-STNVGSNT-Hyp-amide
5165	SEQ ID NO: 64	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-Peg8-Hyp-STNVGSNT-Hyp-amide
5166	SEQ ID NO: 65 SEQ ID NO: 66	CH3CO-Om((COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-mPeg)-STNVOSNT-Hyp-amide
5167	SEQ ID NO: 67 SEQ ID NO: 68	CH3CO-Om((COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-Peg8)-STNVGSNT-Hyp-amide
5168	SEQ ID NO: 69	β K-CNTATCATQRLAEFLRHSS-acid
5169	SEQ ID NO: 70	β K-CNTATCATQRLAEFLRHSSNFGA-acid
5171	SEQ ID NO: 71	β K-CNTATCATQRLAEFLRHSSNNFGAIL-amide
5173	SEQ ID NO: 72	β K-CNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSN-amide
5175	SEQ ID NO: 73 SEQ ID NO: 74 SEQ ID NO: 75	H-Aib-EGTFTSDVSSYLEGQAAKEFIAWLVRGRG-Peg8-Om((β K-CNTATCATQRLAEFLRHSSNNFGAIL-Peg8)STNVGSNT-Hyp-amide
5177	SEQ ID NO: 76	β K-CNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSN-acid
5178	SEQ ID NO: 77	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-Hyp-STNVGSNT-Hyp-acid
5179	SEQ ID NO: 78	β K-CNTATCATQRLAEFLRHSS-Peg8-Hyp-STNVGSNT-Hyp-amide
5186	SEQ ID NO: 79 SEQ ID NO: 80 SEQ ID NO: 81	H(Aib)EGTFTSDVSSYLEGQAAKEFIAWLVRGRG-Peg8-Om((COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNNFGAIL-Peg8)STNVGSNT-Hyp-amide
5187	SEQ ID NO: 82 SEQ ID NO: 83	β K-CNTATCATQRLAEFLRH-Peg10-Hyp-STNVGSNT-Hyp-amide

Fig. 63 (Cont. 2)

5188	SEQ ID NO: 84 SEQ ID NO: 85	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRH-Peg10-Hyp-STNVGSNT-Hyp-amide
5189	SEQ ID NO: 86 SEQ ID NO: 87 SEQ ID NO: 88	H-Aib-EGTFTSDVSSYLEGQAAK(mPeg-mPeg- γ E-COC16H32CO2H)EFIWLVRGRG-Peg8-Om(β K-CNTATCATQRLAEFLRHSSNFGAIL-Peg8)STNVGSNT-Hyp-amide
5190	SEQ ID NO: 89 SEQ ID NO: 90	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSS-Peg8-Hyp-STNVGSNT-Hyp-amide
5191	SEQ ID NO: 91 SEQ ID NO: 92 SEQ ID NO: 93	Y-Aib-QGTFTSDYSI-aMc,L-LDKKAQ-Aib-AFIEYLLLEGGPSSGAPPPS-Peg8-Om((COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSSNFGAIL-Peg8)STNVGSNT-Hyp-amide
5193	SEQ ID NO: 94 SEQ ID NO: 95 SEQ ID NO: 96	H-Aib-EGTFTSDVSSYLEGQAAKEFLWLVRGRG-Peg8-Peg8-K((COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSS-Peg8)STNVGSNT-HYP-amide
5194	SEQ ID NO: 97 SEQ ID NO: 98 SEQ ID NO: 99	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSS-Peg8-K(H-Aib-EGTFTSDVSSYLEGQAAKEFLWLVRGRG-Peg8-Peg8)STNVGSNT-Hyp-amide
5196	SEQ ID NO: 100	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSS-Hyp-STNVGSNT-Hyp-amide
5197	SEQ ID NO: 101 SEQ ID NO: 102 SEQ ID NO: 103	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSS-Peg8-K(H-Arb-EGTFTSDVSSYLEGQAAK(mPeg-mPeg- γ E-OC16H32CO2H))EFIWLVRGRG-Peg8-Peg8)STNVGSNT-Hyp-amide
5198	SEQ ID NO: 104 SEQ ID NO: 105 SEQ ID NO: 106	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSS-Peg8-K(Aib-EGTFTSDVSSYLEGQAAKEAIAWLVRGRG-Peg8-Peg8)STNVGSNT-Hyp-amide
5199	SEQ ID NO: 107 SEQ ID NO: 108 SEQ ID NO: 109	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSS-Peg8-K(Y-Aib-EGTFTSDYSI-Aib-LDKIAQKAFVQWLIAGGPSSGAPPPS-Peg8)STNVGSNT-Hyp-amide
5200	SEQ ID NO: 110 SEQ ID NO: 111 SEQ ID NO: 112	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSS-Peg8-K(Y-Aib-EGTFTSDYSI-Aib-LDKIAQKAFVQWLIAGGPSSGAPPPS-Peg8)STNVGSNT-Hyp-amide
5204	SEQ ID NO: 113 SEQ ID NO: 114	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSS-Peg8-LysN3-STNVGSNT-Hyp-amide
5212	SEQ ID NO: 115 SEQ ID NO: 116 SEQ ID NO: 117	(COOH)C18H36CO- γ E- β K-CNTATCATQRLAEFLRHSS-Peg8-K(Aib-QGTFTSDYSI-aMc,L-LDKKAQ-Aib-AAIEYLLLEGGPSSGAPPPS-Peg8-PGT)STNVGSNT-Hyp-amide

Fig. 63 (Cont. 3)

5213	SEQ ID NO: 118 SEQ ID NO: 119 SEQ ID NO: 120	(COOH)C18H36CO-γE-βK-CNTATCATQRLAEFLRHSS-Peg8-K(Y-Aib-QGTFFTSDYSI-aMe,L-LDKKAAQ-Aib-AFVEYLLEGGPSSGAPPPS -Peg8-PGT)STNVGSNT-Hyp-amide
5214	SEQ ID NO: 121 SEQ ID NO: 122 SEQ ID NO: 123	(COOH)C18H36CO-γE-βK-CNTATCATQRLAEFLRHSS-Peg8-K(Y-Aib-EGT-aMe,F-TSDYSI-Aib-LEKTAAKAFVQWLIAGGPSSGAPPPS -PEG8-PGT)STNVGSNT-Hyp-amide
5215	SEQ ID NO: 124 SEQ ID NO: 125 SEQ ID NO: 126	(COOH)C18H36CO-γE-βK-CNTATCATQRLAEFLRHSS-Peg8-K(Y-Aib-QGTFFTSDYSI-aMe,L-LDKKAAQ-Aib-AFVQWLLLEGGPSSGAPPPS -Peg8-PGT)STNVGSNT-Hyp-amide
5233	SEQ ID NO: 127 SEQ ID NO: 128 SEQ ID NO: 129	(COOH)C18H36CO-γE-βK-CNTATCATQRLAEFLRHSS-Peg8-K(Y-Aib-QGTFFTSDYSI-aMe,L-LDKKAAQ-Aib-AFVQWLLLEGGPSSGAPPPS -Peg8-Cys-CH2CO)STNVGSNT-Hyp-amide
5234	SEQ ID NO: 130 SEQ ID NO: 131 SEQ ID NO: 132	(COOH)C18H36CO-γE-βK-CNTATCATQRLAEFLRHSS-Peg8-K(Y-Aib-QGTFFTSDYSI-aMe,L-LDKKAAQ-Aib-AFVQWLLLEGGPSSGAPPPS -Peg8-Cys[S-S]Cys)STNVGSNT-Hyp-amide
5235	SEQ ID NO: 133 SEQ ID NO: 134 SEQ ID NO: 135	(COOH)C18H36CO-γE-βK-CNTATCATQRLAEFLRHSS-Peg8-K(Y-Aib-QGTFFTSDYSI-aMe,L-LDKKAAQ-Aib-AFVQWLLLEGGPSSGAPPPS -Peg8-Cys[S-S]Pen)STNVGSNT-Hyp-amide
5239	SEQ ID NO: 136 SEQ ID NO: 137 SEQ ID NO: 138	(COOH)C18H36CO-γE-βK-CNTATCATQRLAEFLRHSS-Peg8-K(Aib-QGTFFTSDYSI-aMe,L-LDKKAAQ-AibAAVQWLLLEGGPSSGAPPPS -Peg8-PGT)STNVGSNT-Hyp-amide
5240	SEQ ID NO: 139 SEQ ID NO: 140 SEQ ID NO: 141	(COOH)C18H36CO-γE-βK-CNTATCATQRLAEFLRHSS-Peg8-K(Y-Aib-QGTFFTSDYSI-aMe,L-LDKKAAQ-Aib-AFVQWLLLEGGPSSGAPPPS -Peg8-PGT)STNVGSNTY-acid
Sema	SEQ ID NO: 142	H-Aib-EGTFTSDV SSYLEGQAAK EFIAWLVRGR G