

FIG. 1

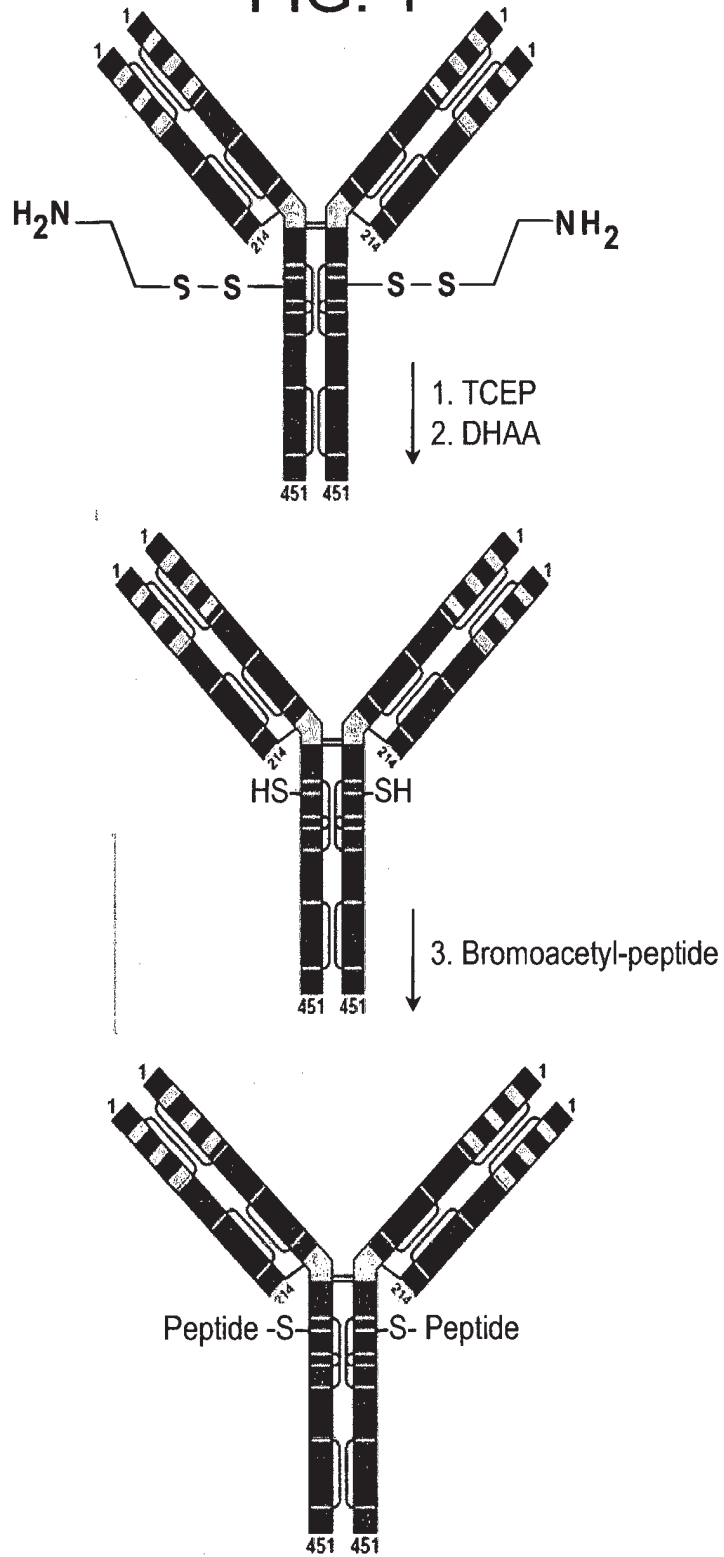


FIG. 2A

GLP1 cAMP assay in ChoK1 hGLP1R clone H20

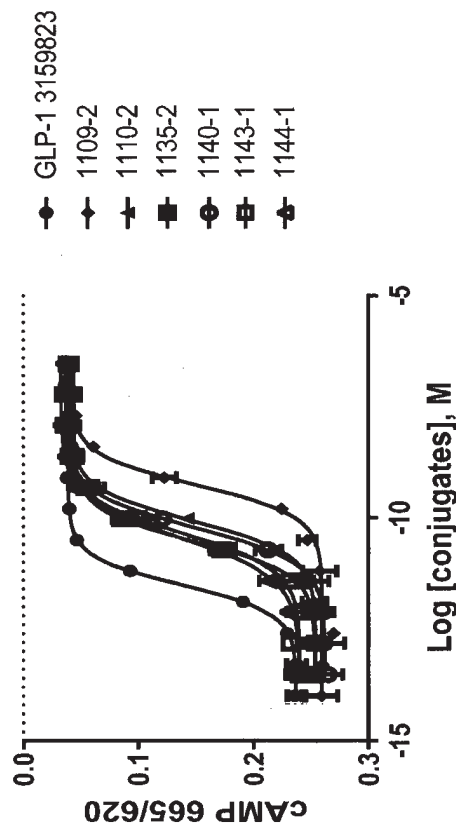


FIG. 2C

GLP1 cAMP assay in ChoK1 hGLP1R clone H20

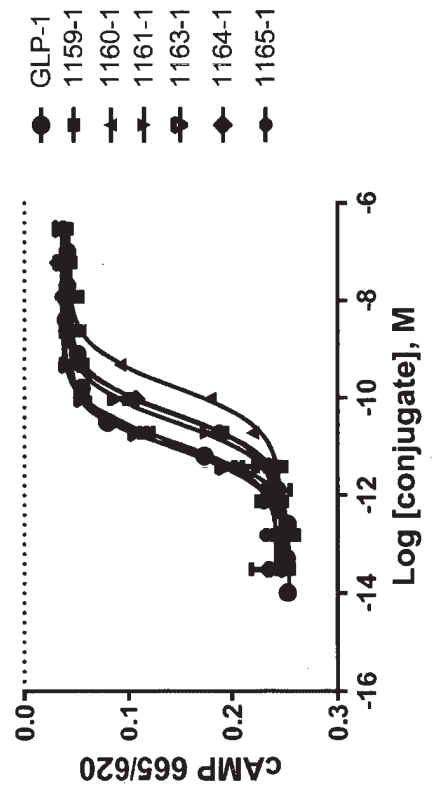


FIG. 2B

GIPR antagonist cAMP assay in 293T/huGIPR clone10

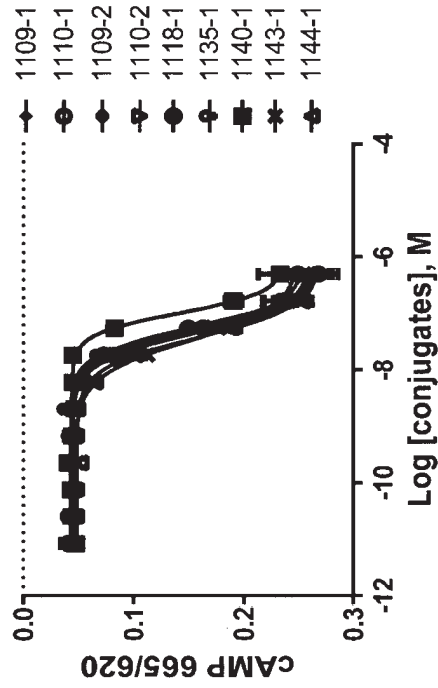


FIG. 2D

GIPR cAMP assay in 293T/huGIPR clone10

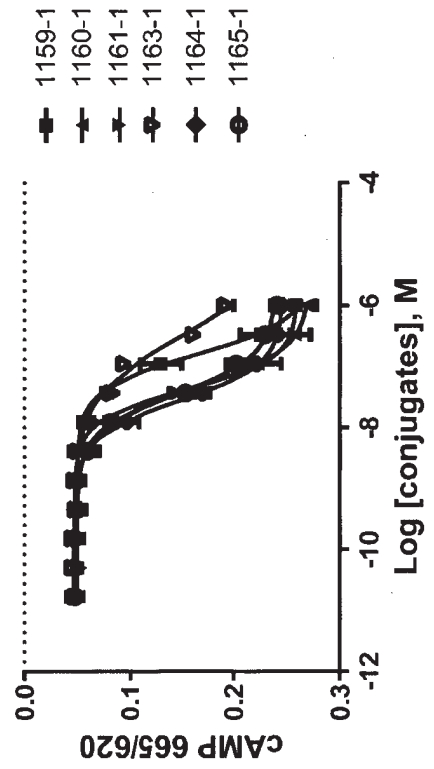


FIG. 2E

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20

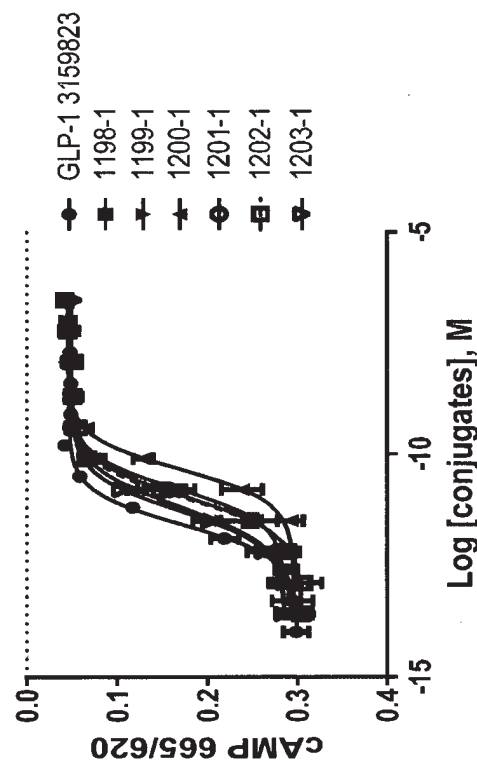


FIG. 2F

cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10

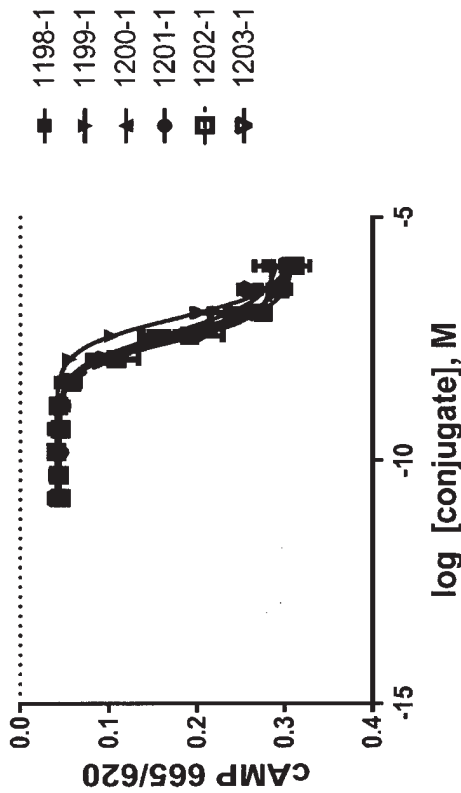


FIG. 2G

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20

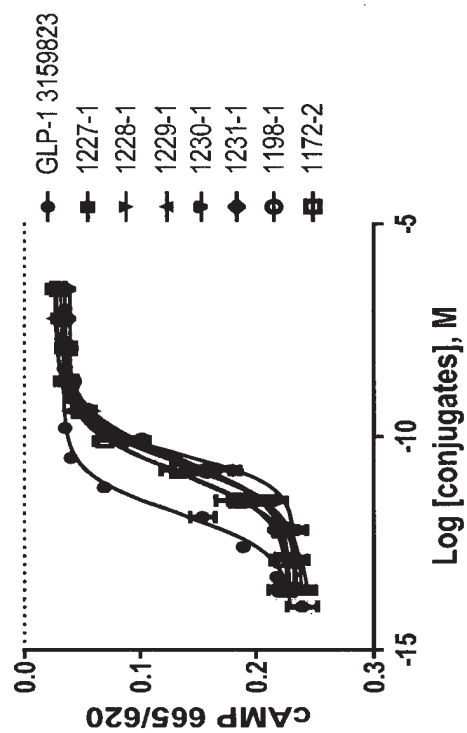


FIG. 2H

cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10

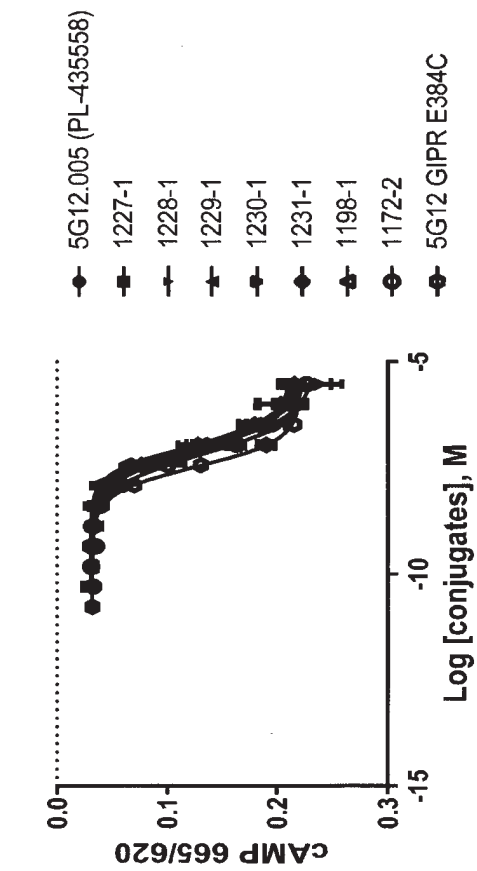


FIG. 2I

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20

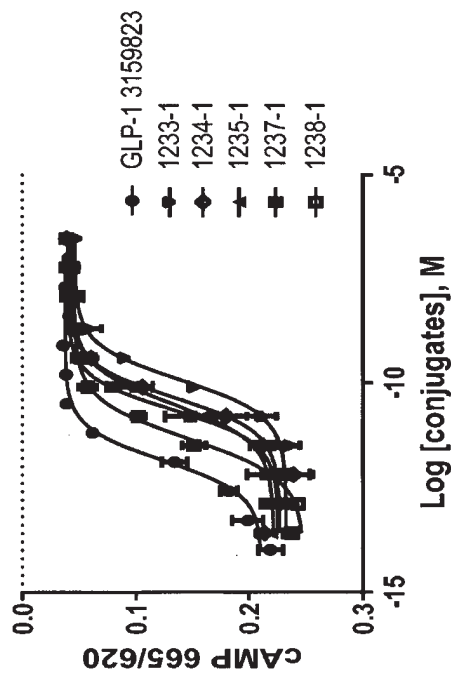


FIG. 2J

cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10

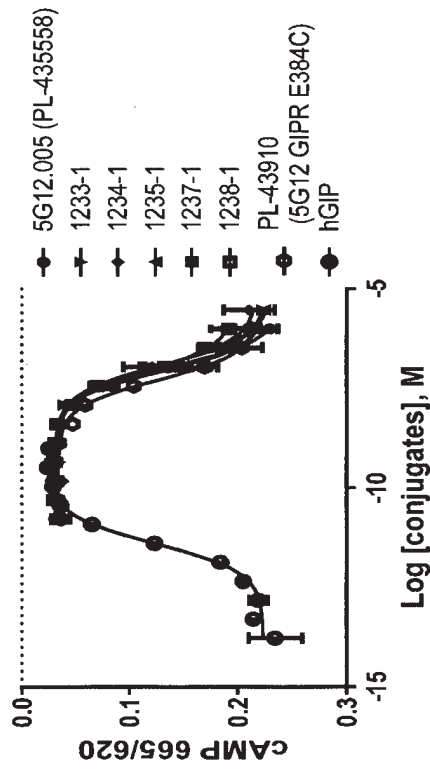


FIG. 2K

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20

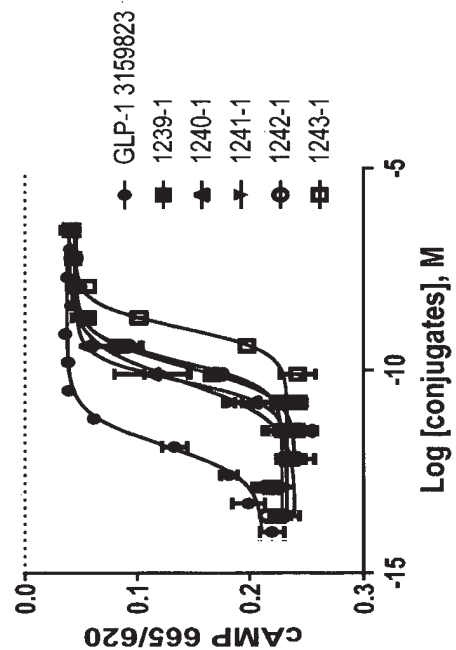


FIG. 2L

cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10

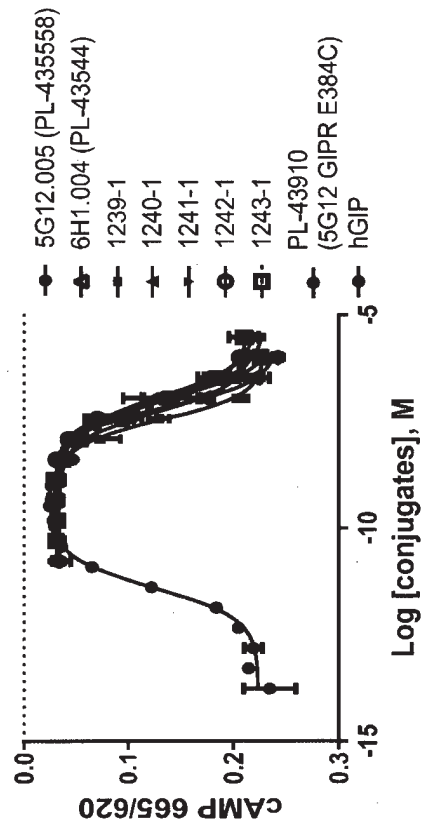
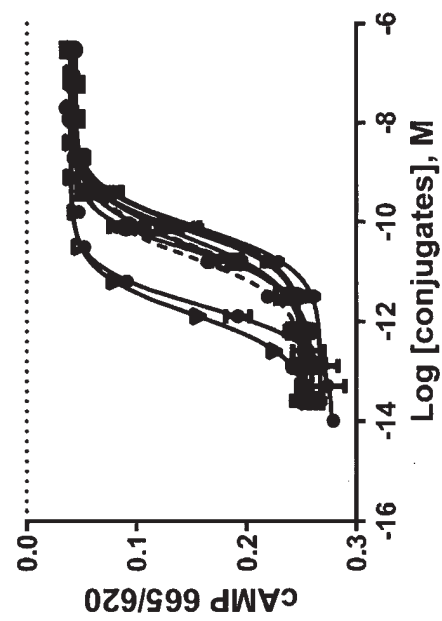
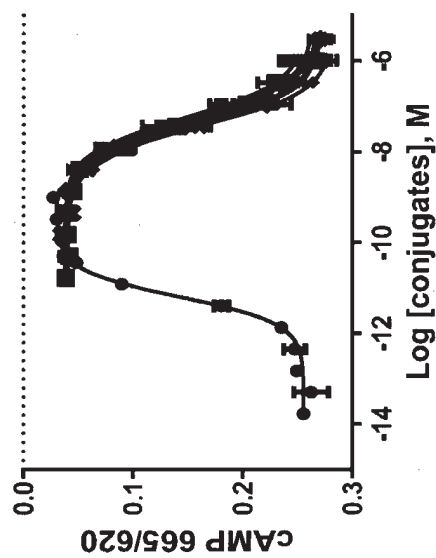


FIG. 2M

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20: cAMP assay (GIPR antagonist mode) in 293T/hGIPR #10
Chemical Conjugates on 5G12



- GLP-1 3159823
Exendin-4
1160-4
1172-1
1227-3
1231-2
1234-1
1238-1
1250-2
1252-1

- hGIP
 ■ 5G12.005 (PL-43558)
 ▬ 1160-4
 ◆ 1172-1
 ● 1227-3
 ✱ 1231-2
 ● 1234-1
 ▬ 1238-1
 ● 1250-2
 ✱ 1252-1

GLP-1 3159823
Exendin-4
1253-2
1254-2
1269-1
1270-1
1283-1
1284-1

FIG. 2Q

cAMP assay (GLP-1 agonist mode) in CHOK1
hGLP1R H20: Chemical Conjugates on 2G10

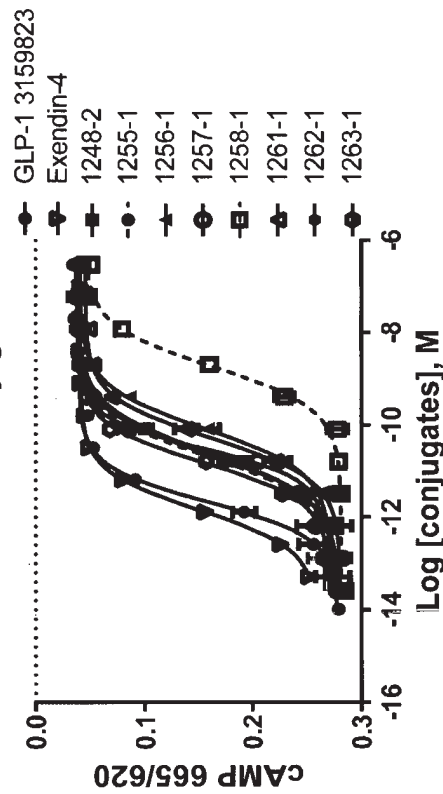


FIG. 2S

cAMP assay (GLP-1 agonist mode) in CHOK1
hGLP1R H20: Chemical Conjugates on 2G10

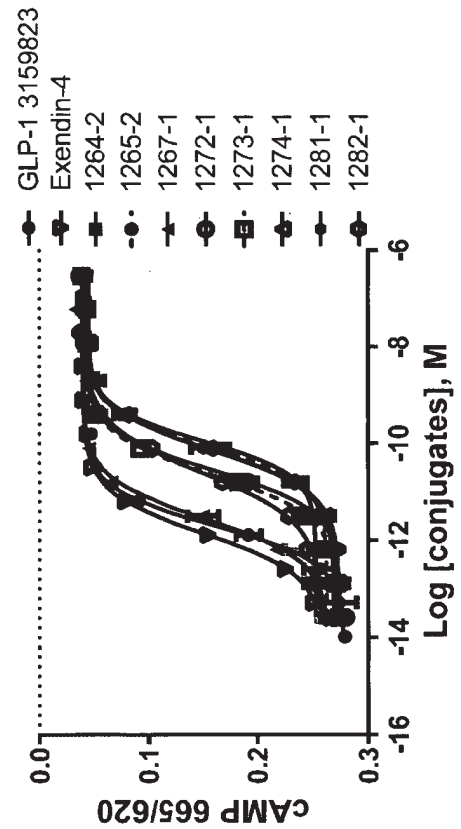


FIG. 2R

cAMP assay (GIPR antagonist mode) in
293T/hGIPR #10 Chemical Conjugates on 2G10

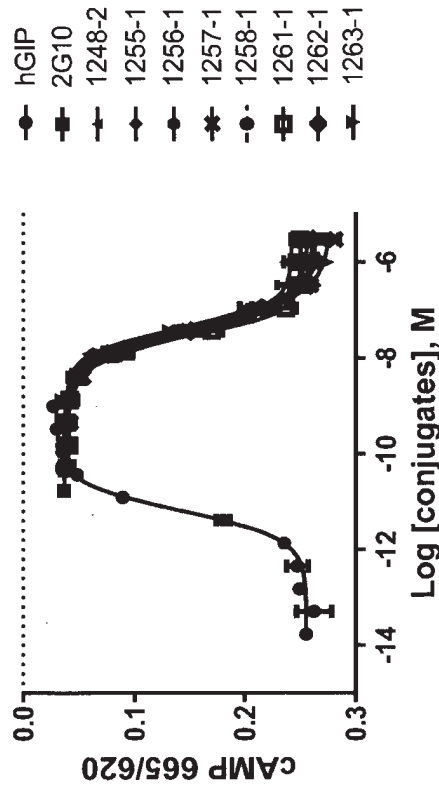


FIG. 2T

cAMP assay (GIPR antagonist mode) in
293T/hGIPR #10 Chemical Conjugates on 2G10

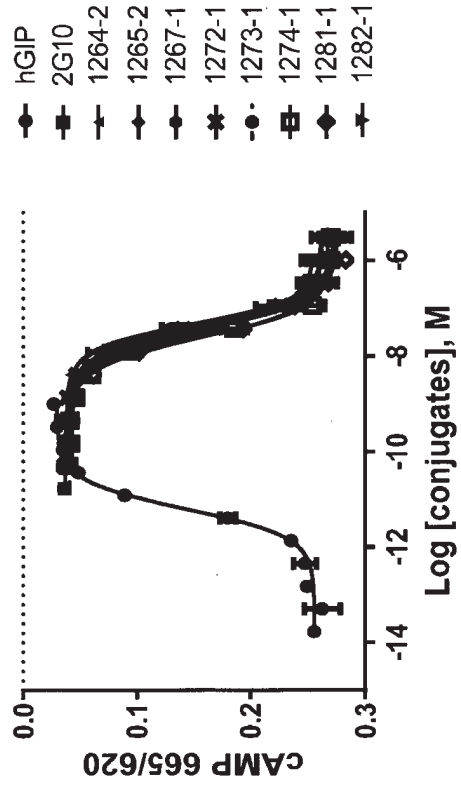
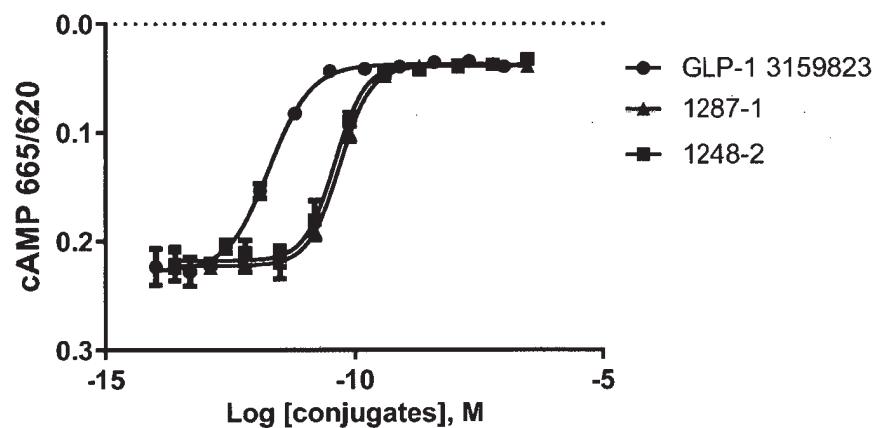


FIG. 3A

Reg #	Description	Peptide information	CHOK1 hGLP-1R	CHOK1 hGLP-1R/GIPR
1148	3166119-E384C-2G10	[Aib8,22;Gly36]GLP-1(7-37)[(G4S)3(BrAc)]	0.04 nM	0.0008 nM
1187	3166119-E384C-aDNP	[Aib8,22;Gly36]GLP-1(7-37)[(G4S)3(BrAc)]	0.05nM	0.08 nM

FIG. 3B

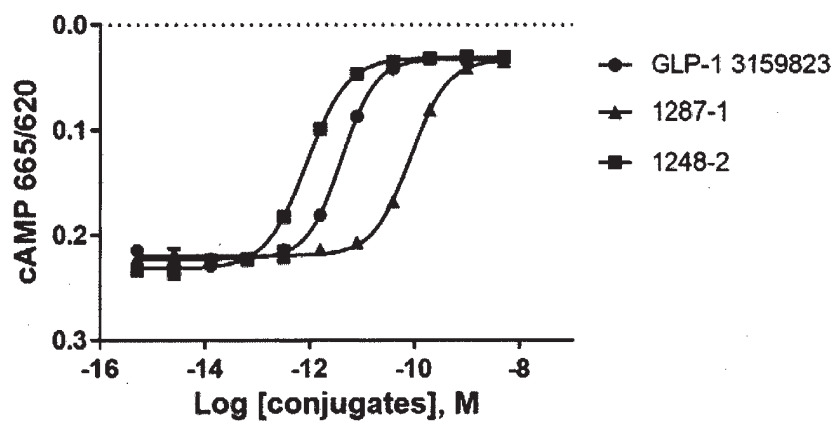
cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R H20:



	GLP-1 3159823	1287-1	1248-2
EC50	1.990e-012	4.963e-011	4.010e-011

FIG. 3C

cAMP assay (GLP-1 agonist mode) in CHOK1 hGLP1R/hGIPR M1 :



	GLP-1 3159823	1287-1	1248-2
EC50	4.091e-012	8.573e-011	8.793e-013

FIG. 4A

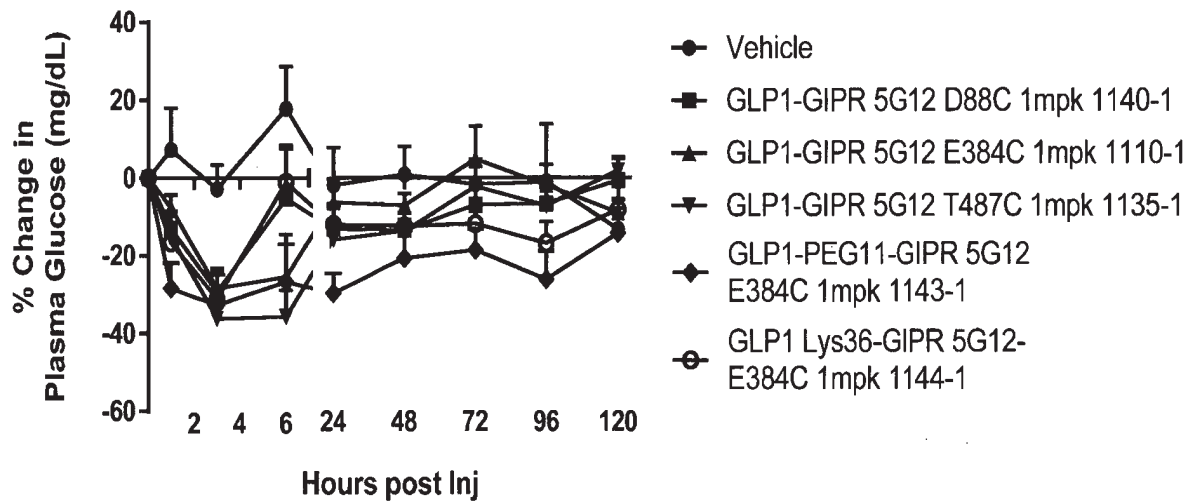


FIG. 4B

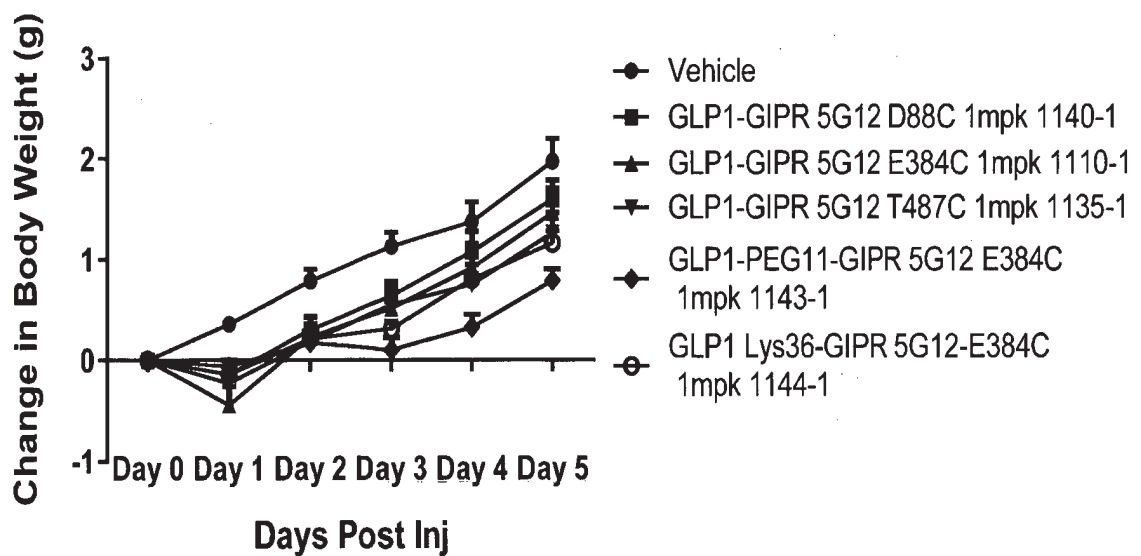


FIG. 4C

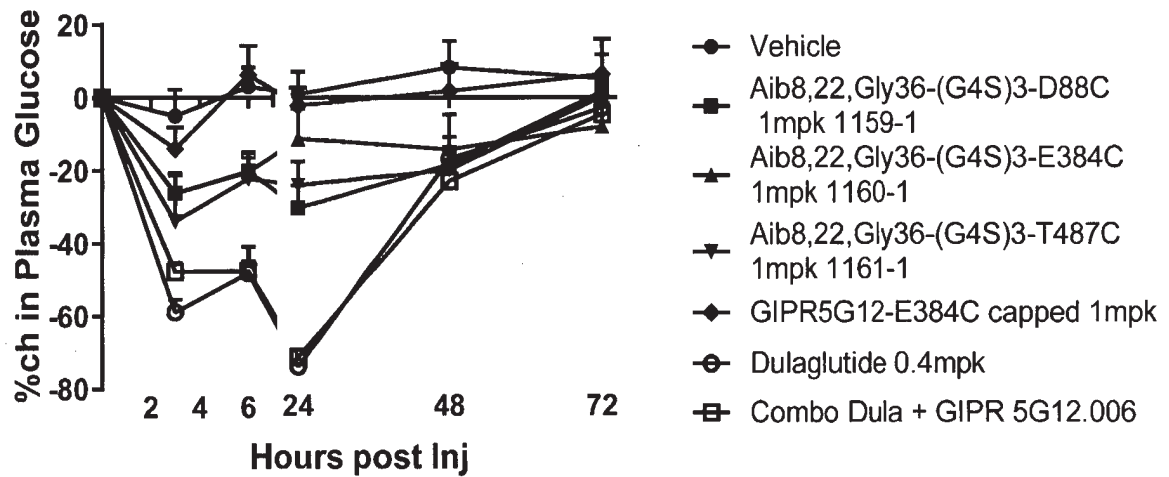


FIG. 4D

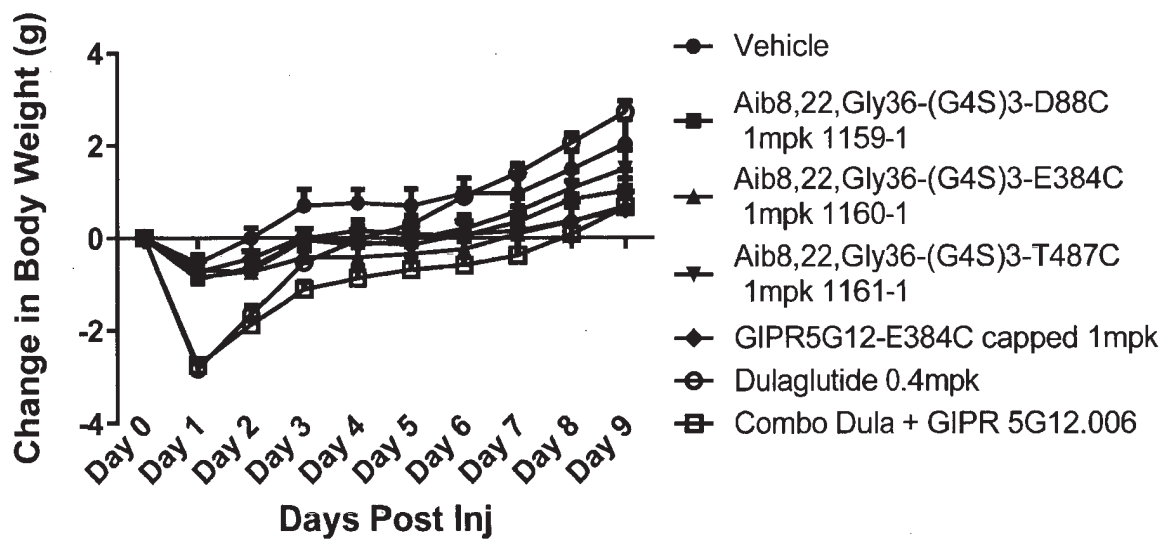


FIG. 4E

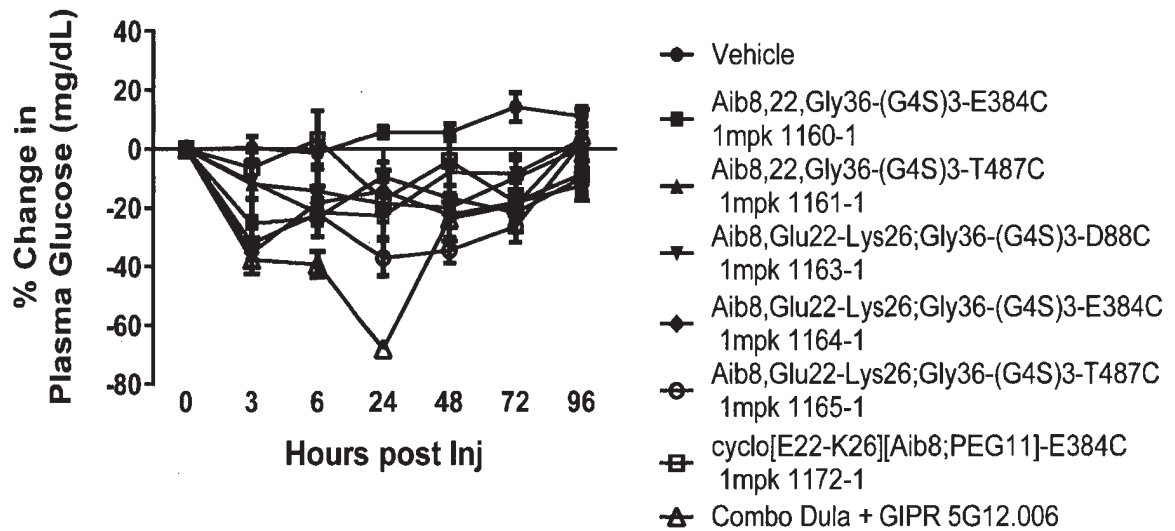


FIG. 4F

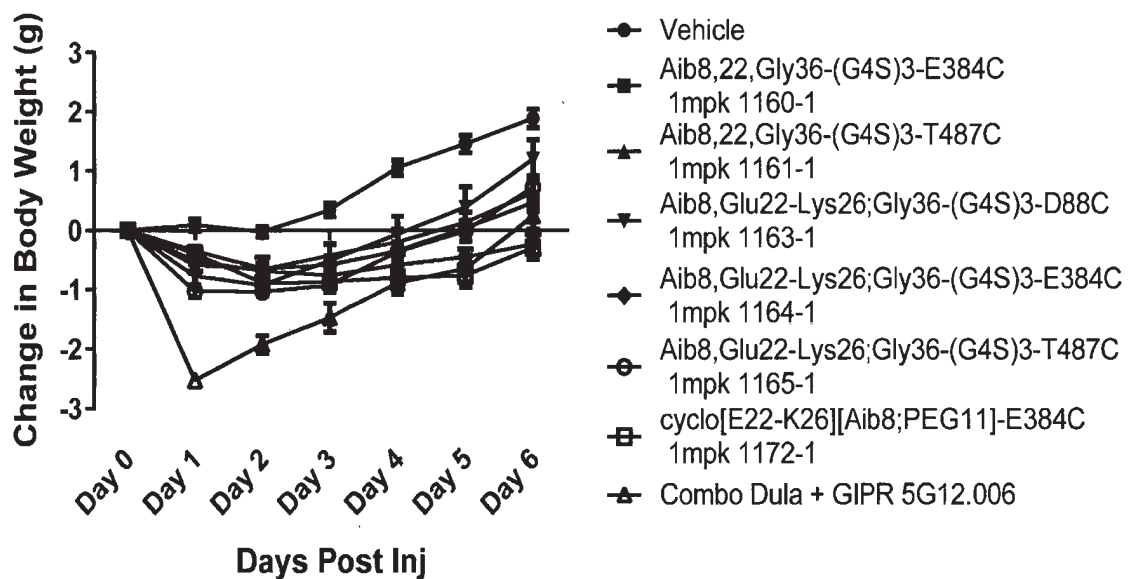


FIG. 4G

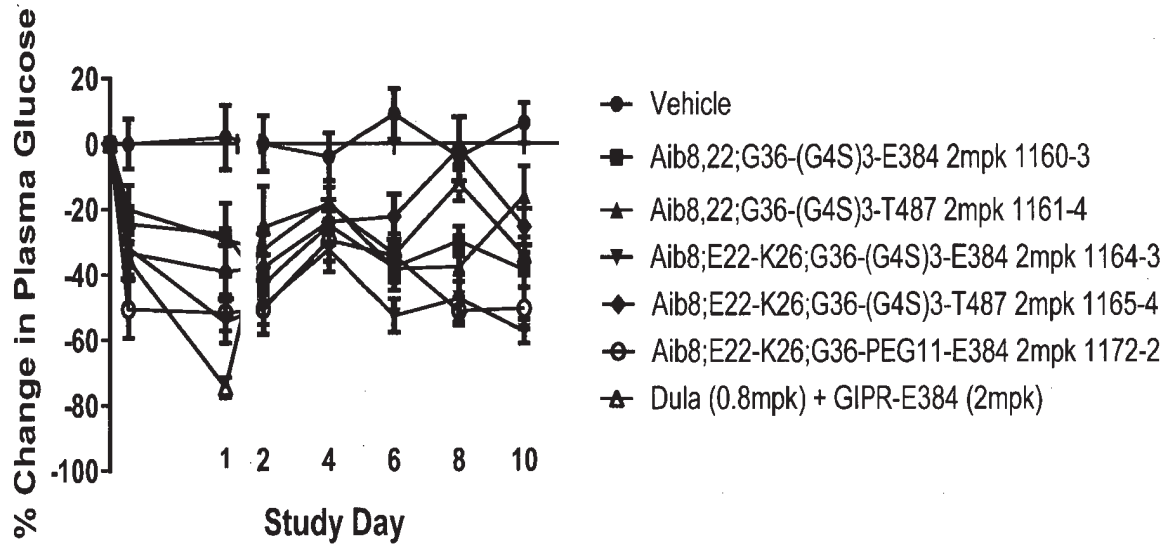


FIG. 4H

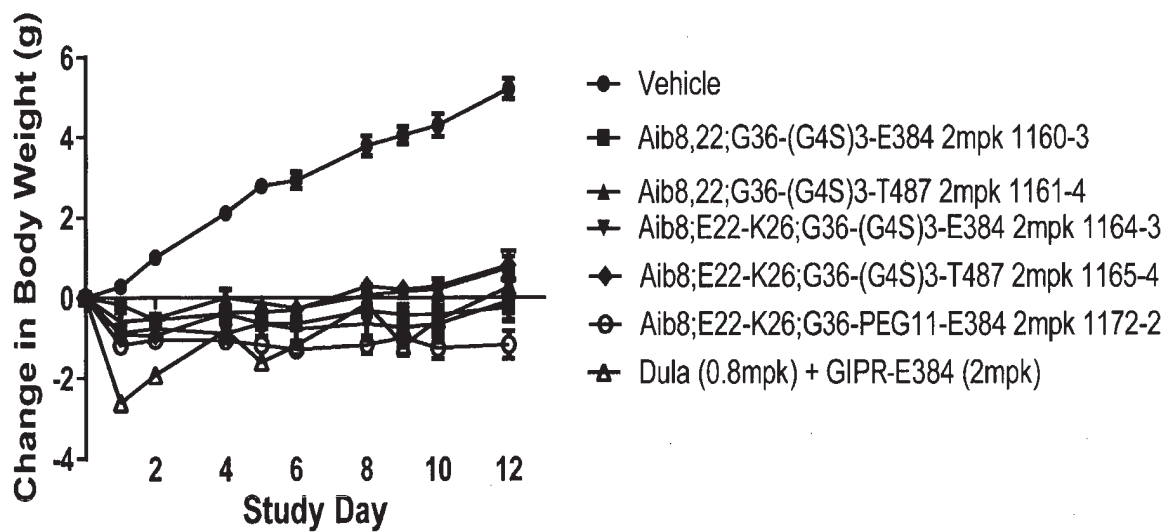


FIG. 4I

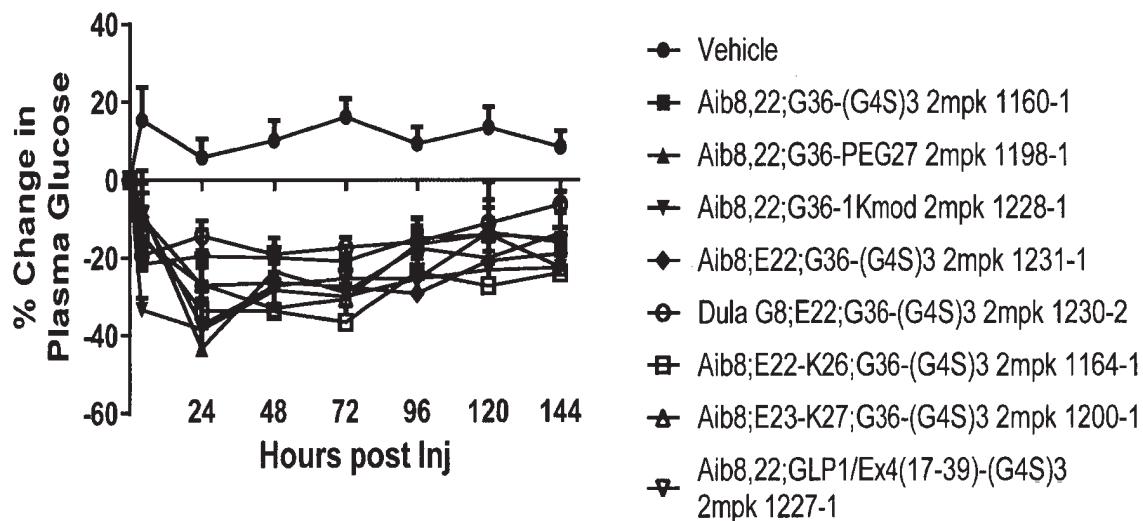


FIG. 4J

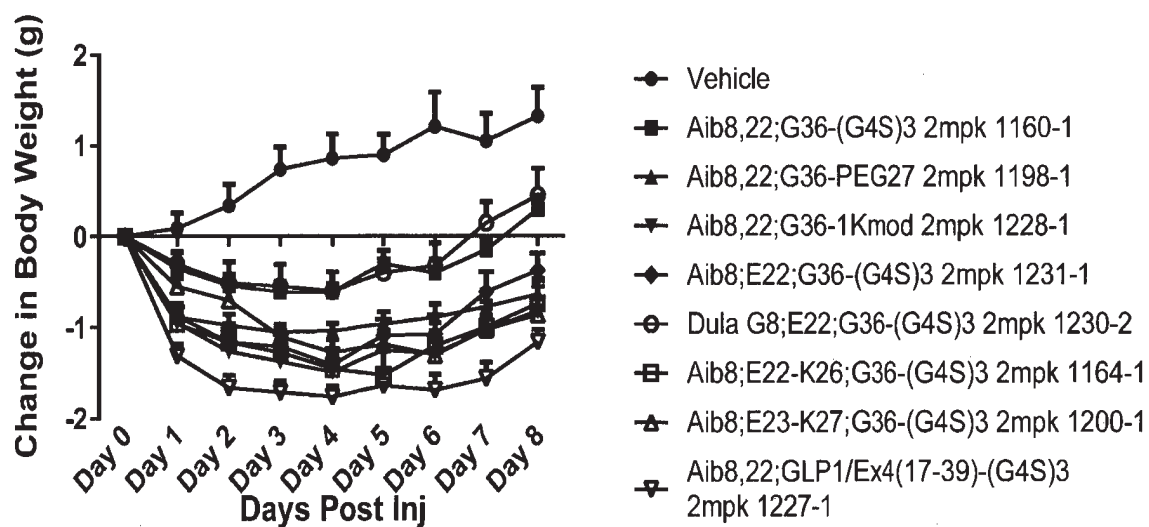


FIG. 4K

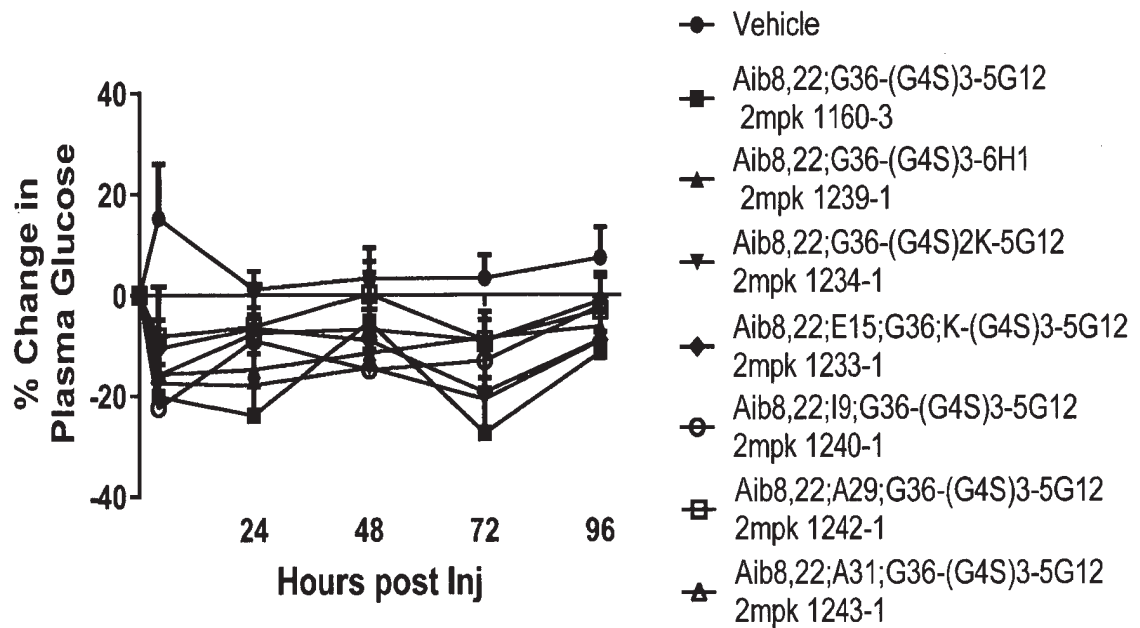


FIG. 4L

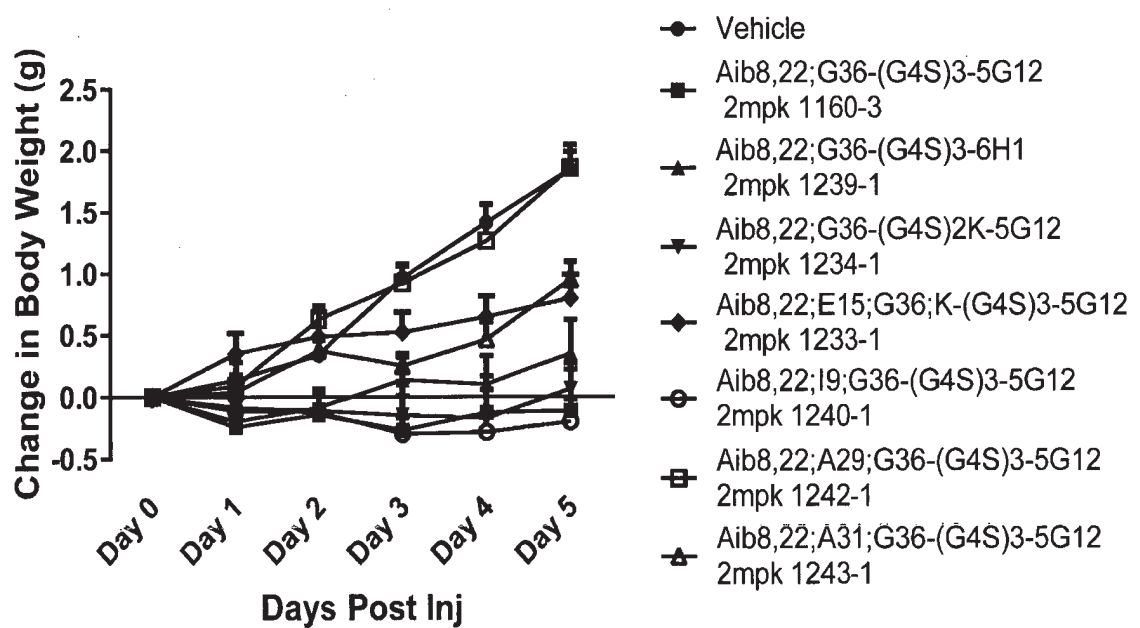


FIG. 4M

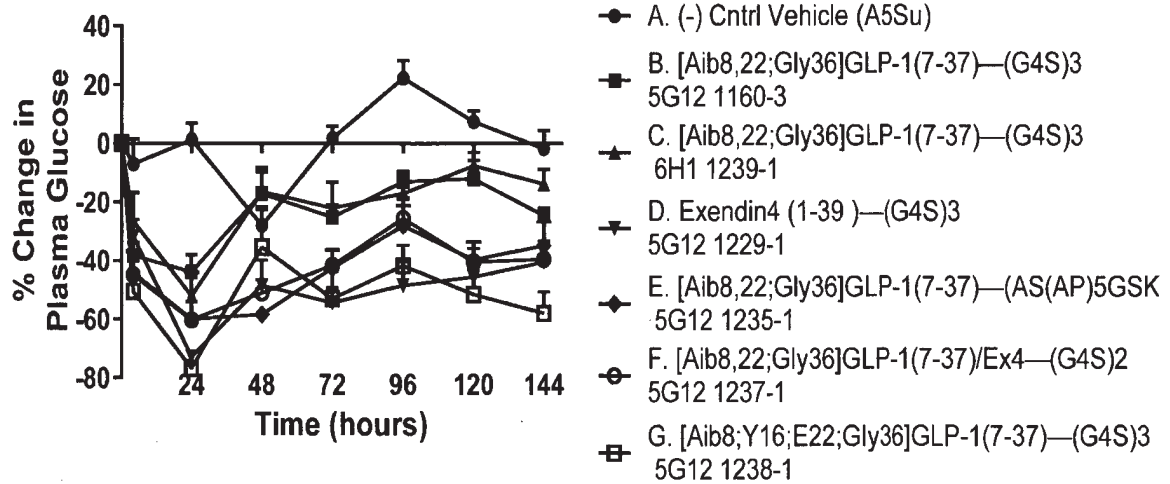


FIG. 4N

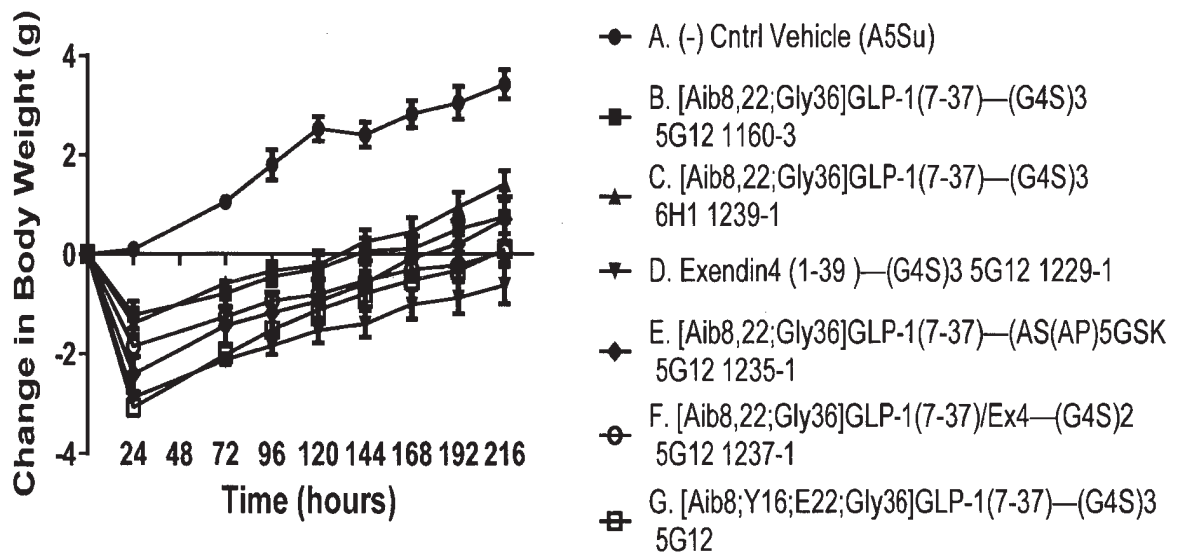


FIG. 4O

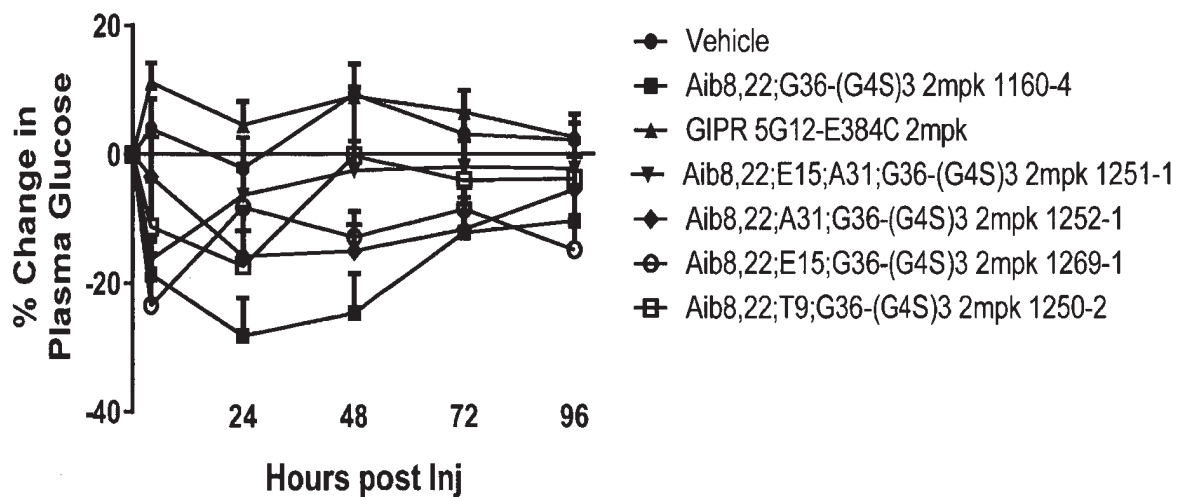
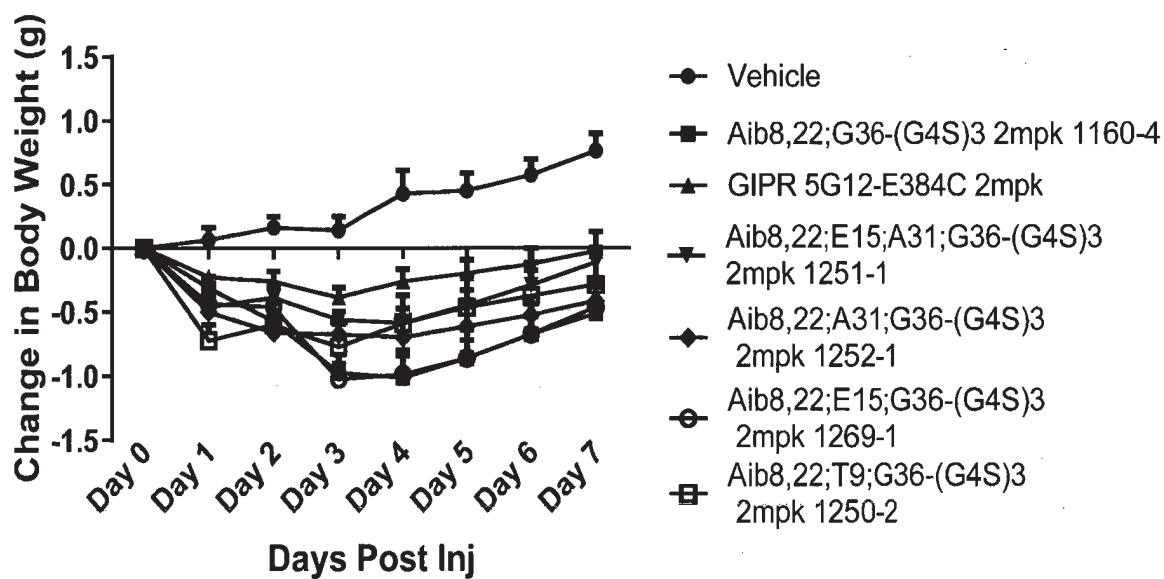


FIG. 4P



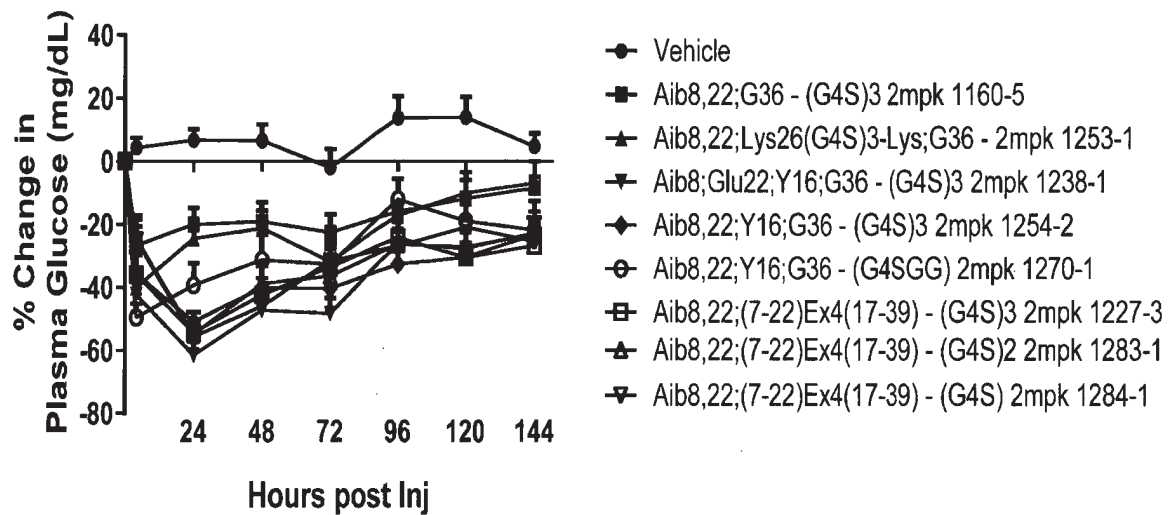
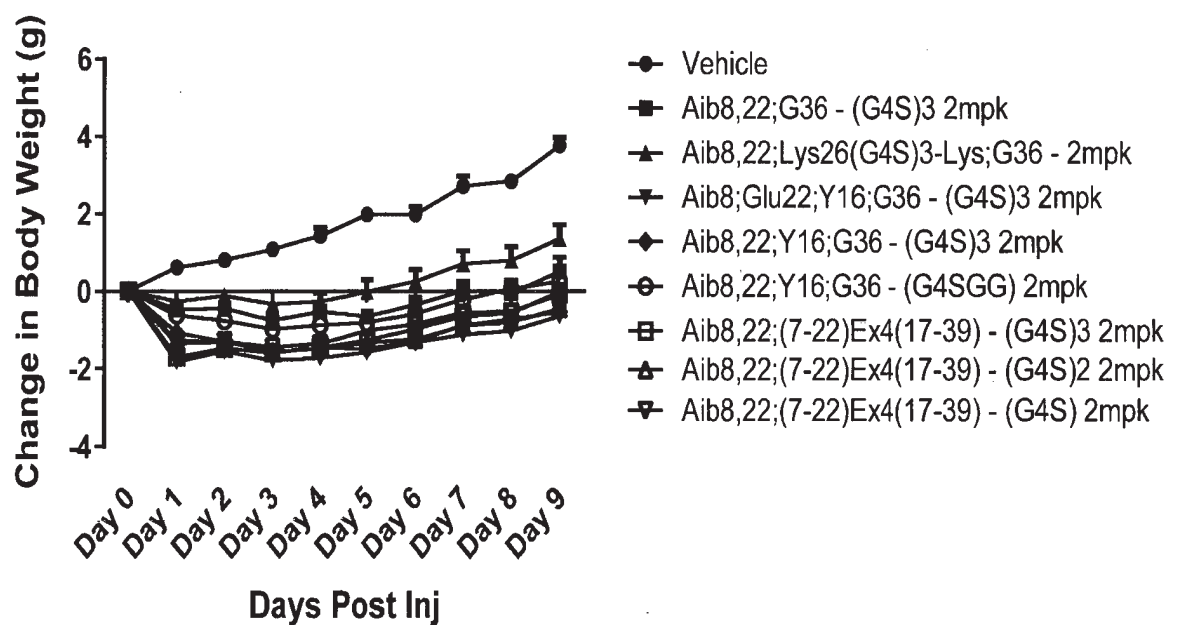


FIG. 5A

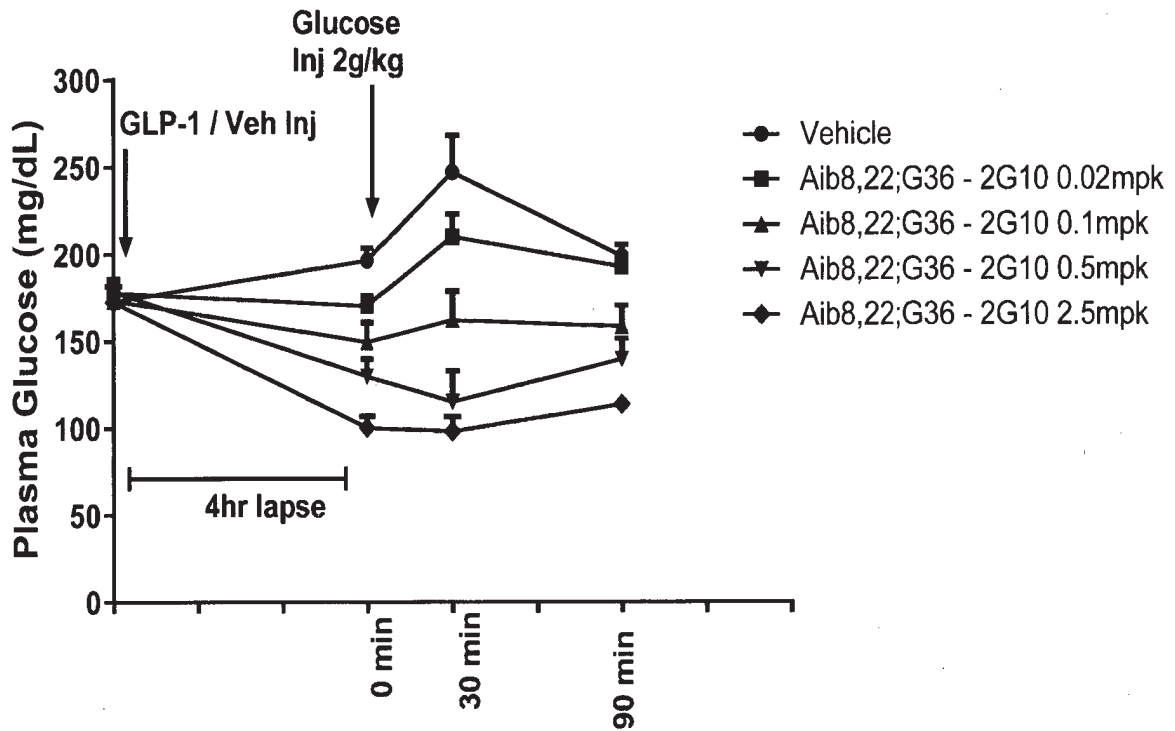


FIG. 5B

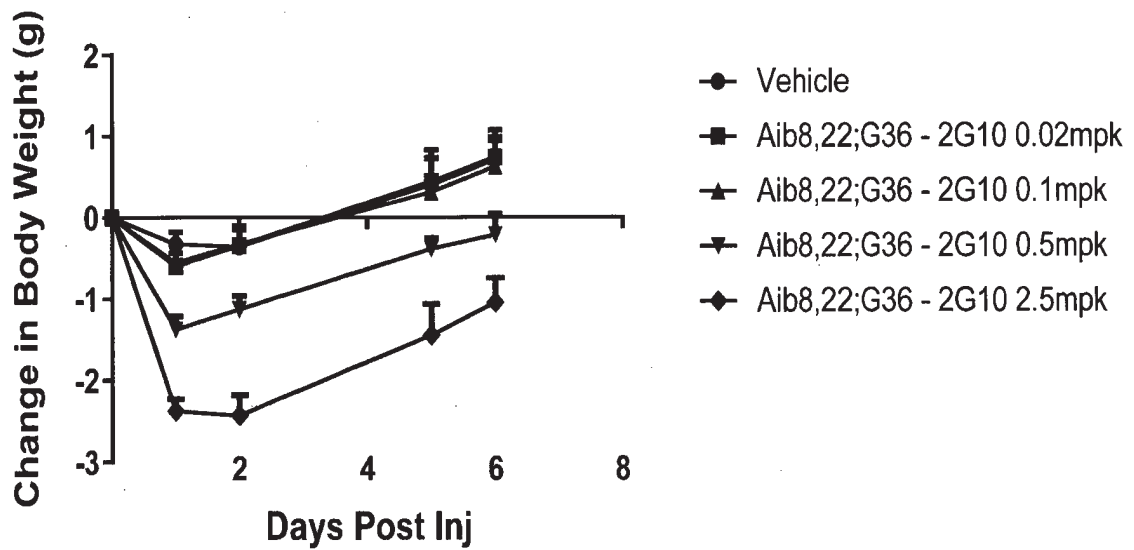


FIG. 5C

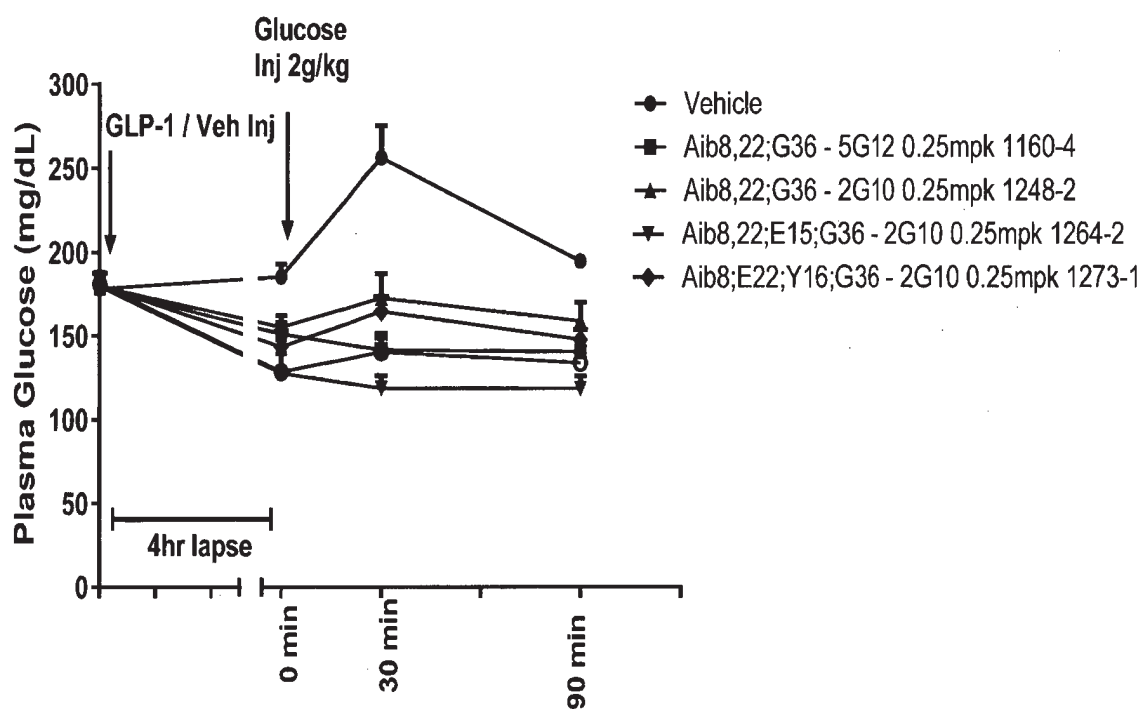


FIG. 5D

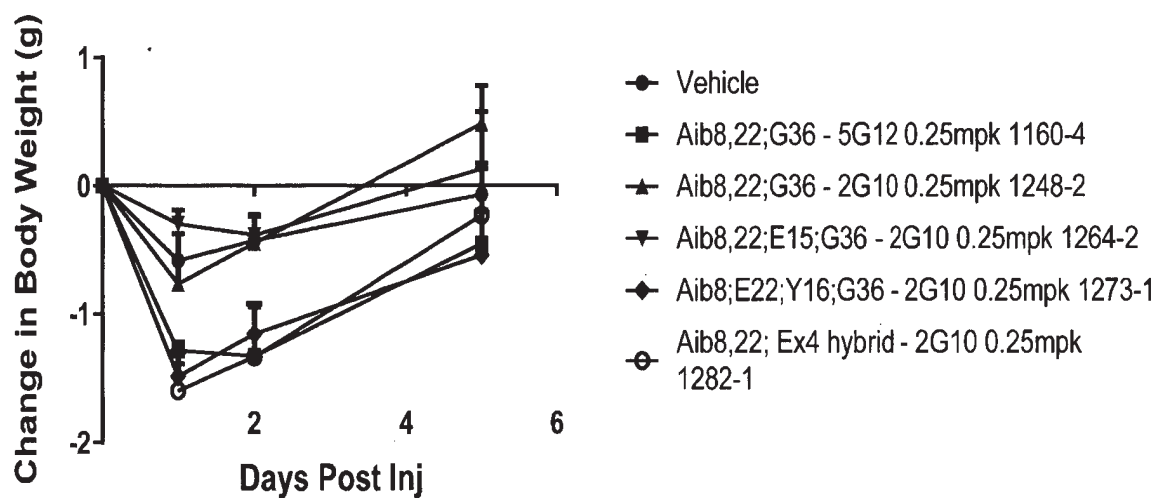


FIG. 6A

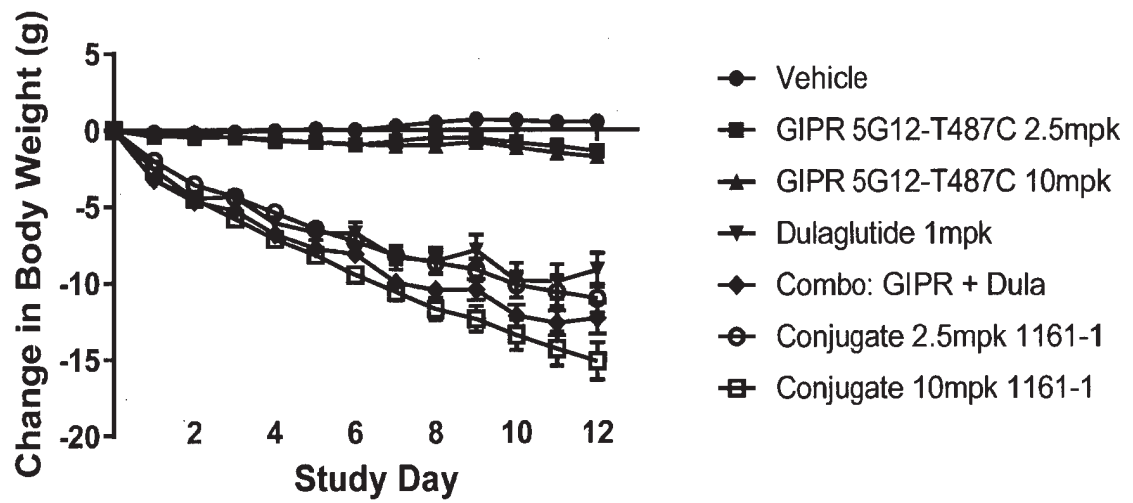


FIG. 6B

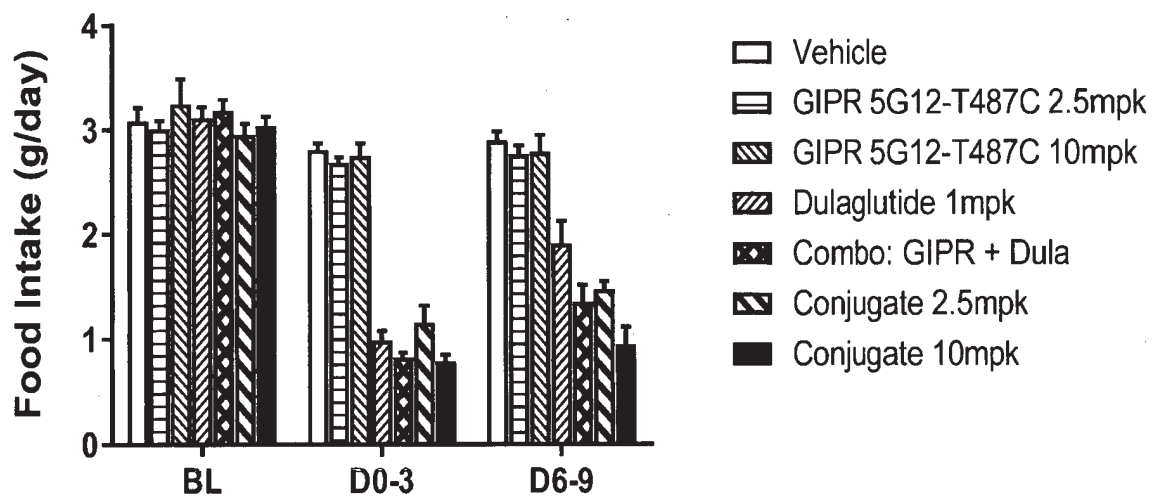
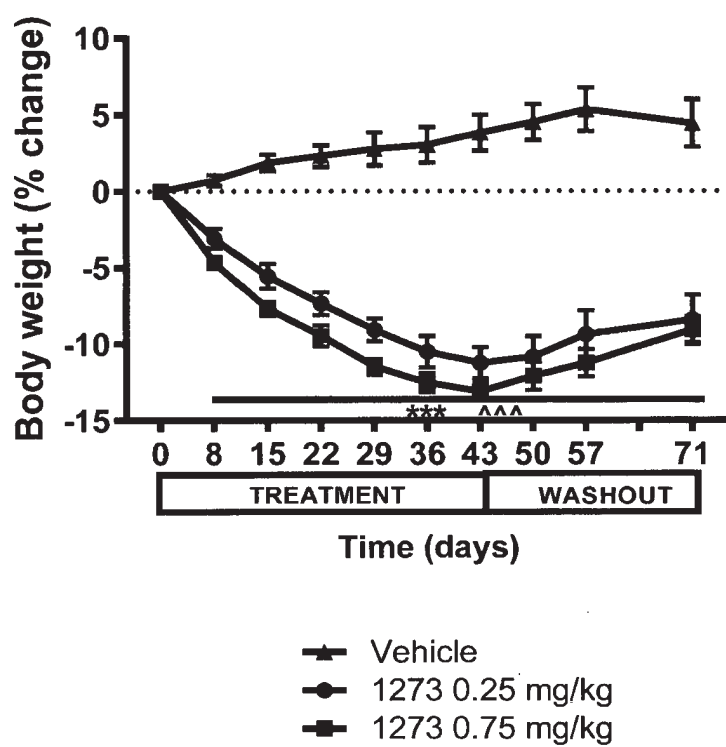
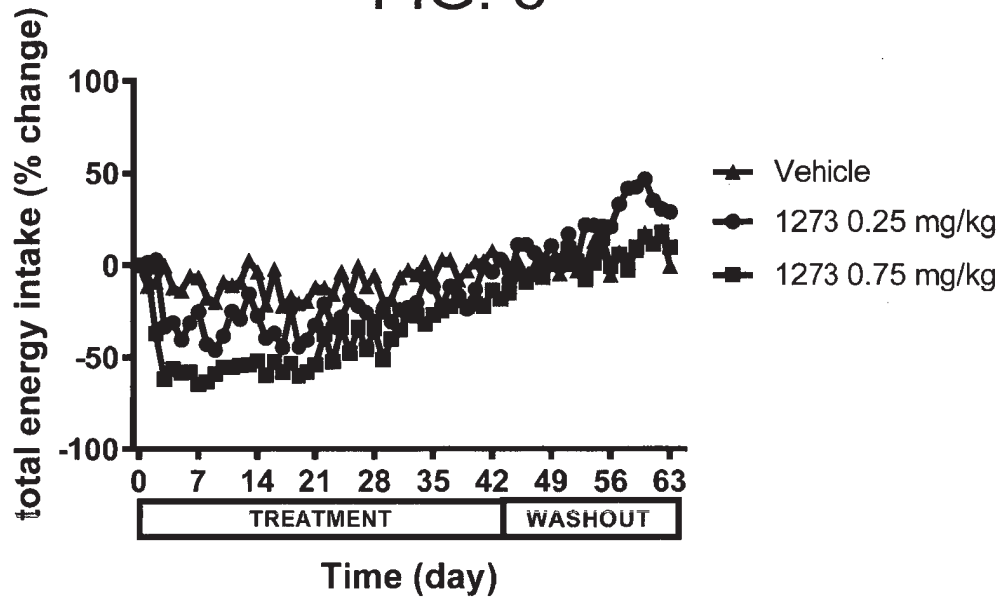


FIG. 7



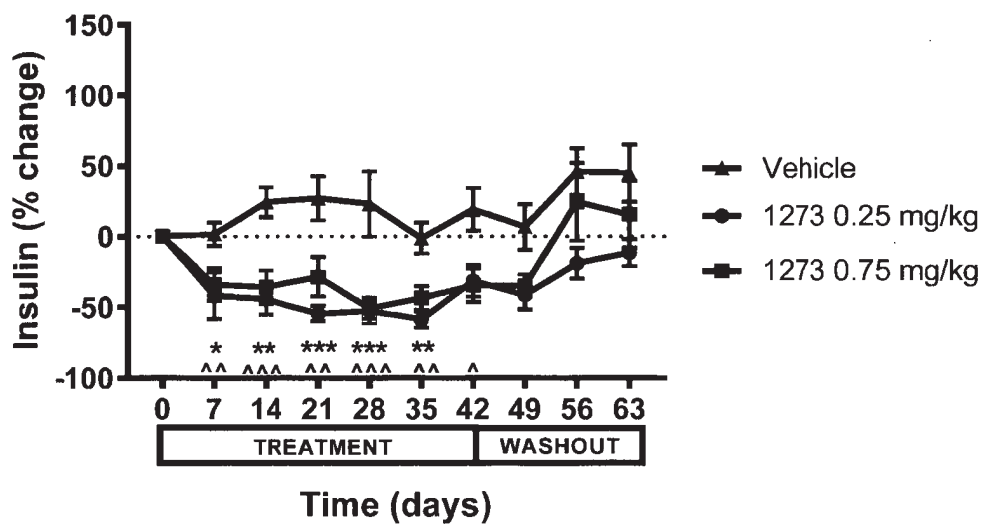
ANCOVA; ***p<0.001 vs vehicle for 0.25 mg/kg; ^^^p<0.001 vs vehicle for 0.75 mg/kg
Data represented as group mean $\pm$ SEM; n=8-9/group

FIG. 8



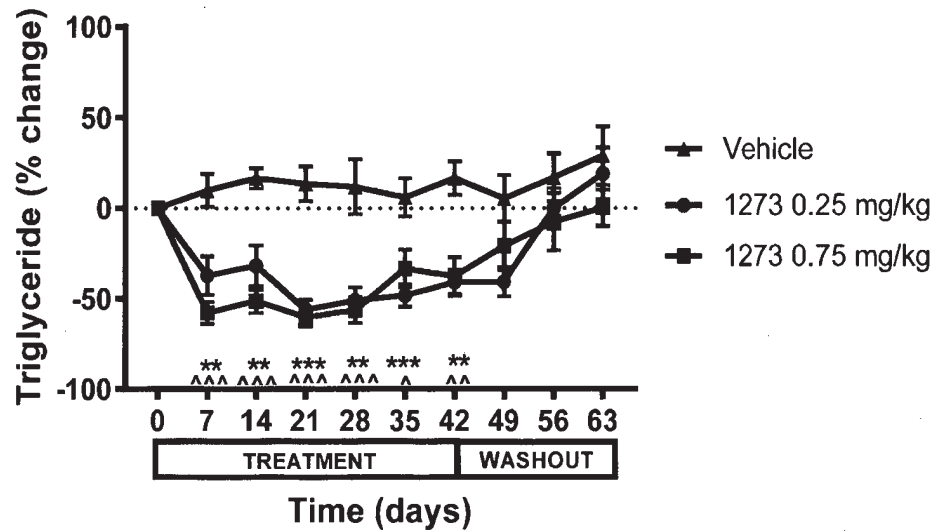
Statistical analysis not performed on total energy intake; error bars not shown; data represented as group mean; n=8-9/group

FIG. 9



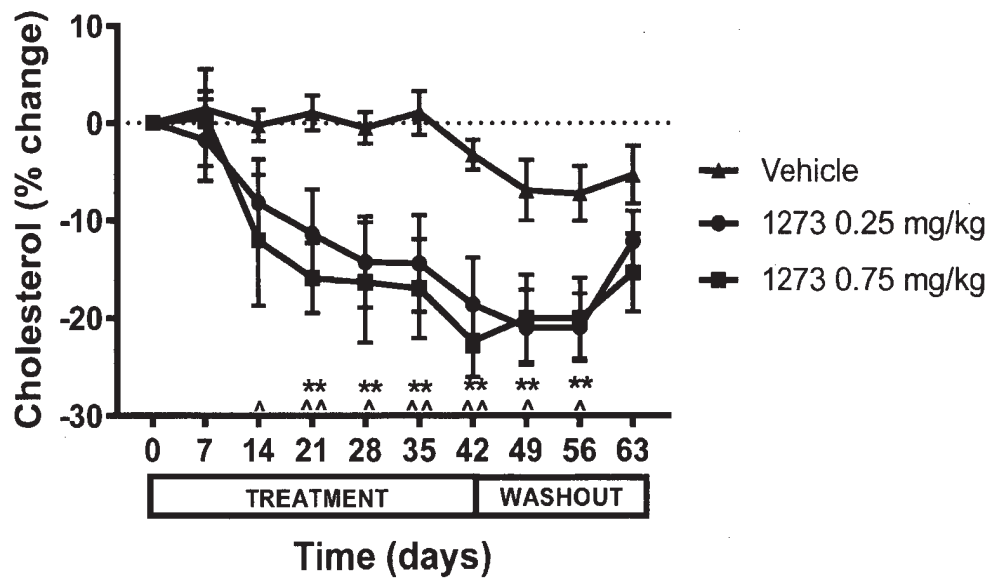
ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehicle for 0.25 mg/kg; ^ $p < 0.05$, ^^ $p < 0.01$, ^^ $p < 0.001$ vs vehicle for 0.75 mg/kg Data represented as group mean $\pm$ SEM; n=8-9/group

FIG. 10



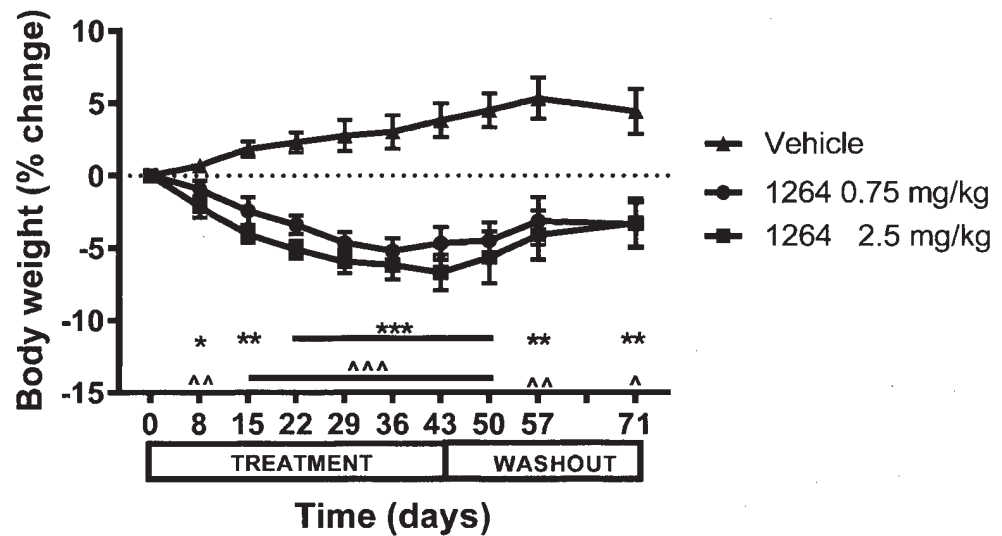
ANCOVA; **p<0.01, ***p<0.001 vs vehicle for 0.25 mg/kg; ^p<0.05, ^^p<0.01, ^^^p<0.001 vs vehicle or 0.75 mg/kg Data represented as group mean $\pm$ SEM; n=8-9/group

FIG. 11



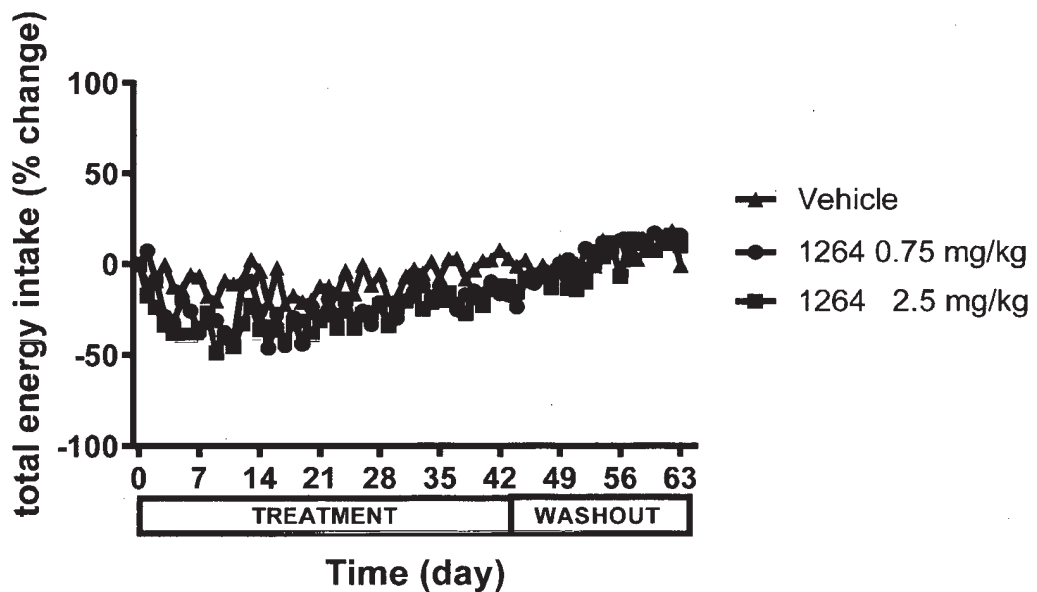
ANCOVA; **p<0.01 vs vehicle for 0.25 mg/kg; ^p<0.05, ^^p<0.01 vs vehicle for 0.75 mg/kg Data represented as group mean $\pm$ SEM; n=8-9/group

FIG. 12



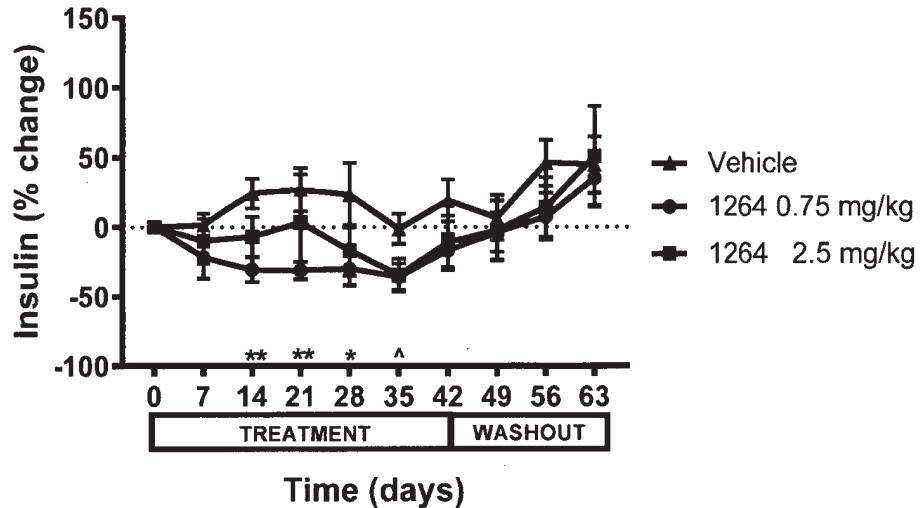
ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehicle for 0.75 mg/kg; ^ $p < 0.05$, ^^ $p < 0.01$, ^^ $p < 0.001$ vs vehicle for 2.5 mg/kg Data represented as group mean $\pm$ SEM; $n=9/\text{group}$

FIG. 13



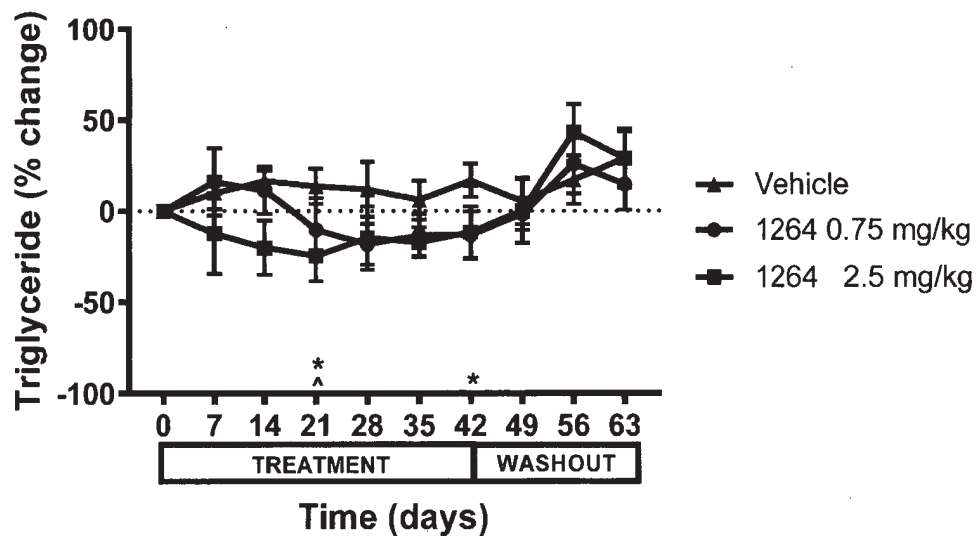
Statistical analysis not performed on total energy intake; error bars not shown; data represented as group mean; $n=9/\text{group}$

FIG. 14



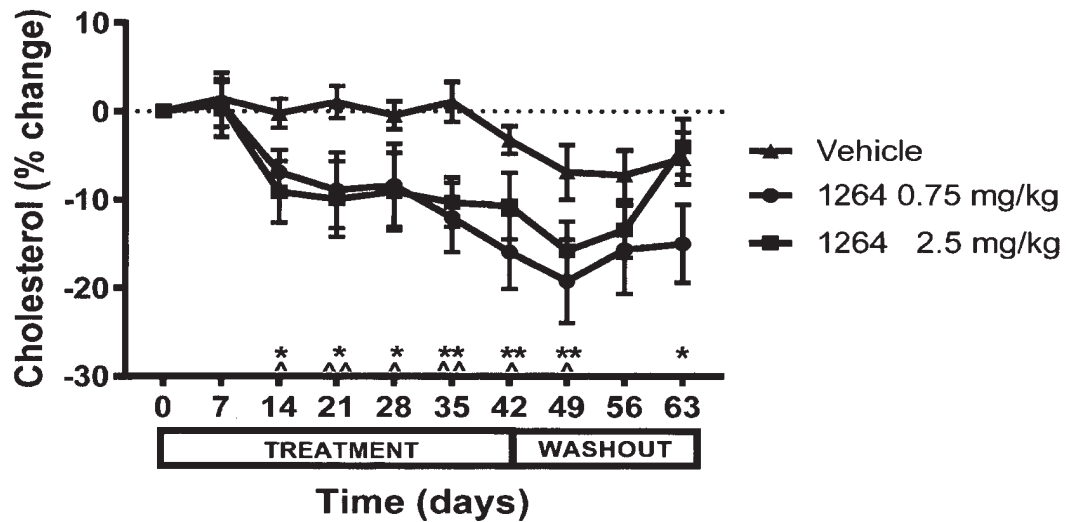
ANCOVA; * $p < 0.05$, ** $p < 0.01$ vs vehicle for 0.75 mg/kg; ^ $p < 0.05$ vs vehicle for 2.5 mg/kg
Data represented as group mean $\pm$ SEM; $n = 9/\text{group}$

FIG. 15



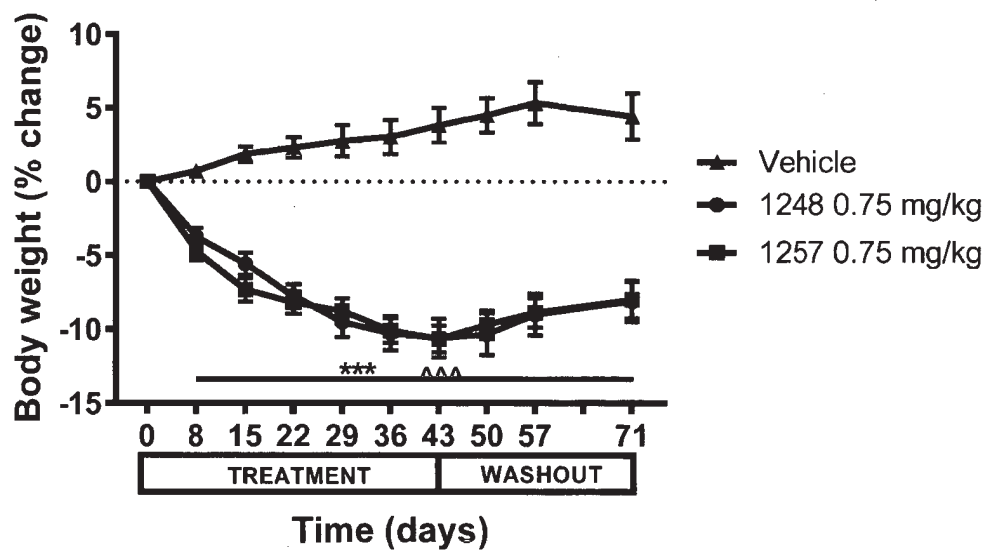
ANCOVA; * $p < 0.05$ vs vehicle for 0.75 mg/kg; ^ $p < 0.05$ vs vehicle for 2.5 mg/kg
Data represented as group mean $\pm$ SEM; $n = 9/\text{group}$

FIG. 16



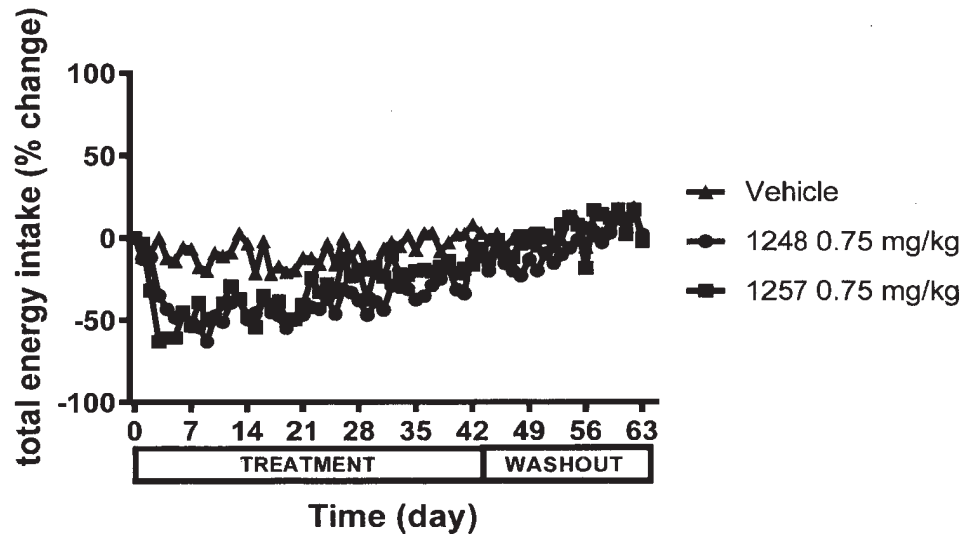
ANCOVA; * $p < 0.05$, ** $p < 0.01$ vs vehicle for 0.75 mg/kg; ^ $p < 0.05$, ^^ $p < 0.01$ vs vehicle for 2.5 mg/kg Data represented as group mean $\pm$ SEM; $n = 9/\text{group}$

FIG. 17



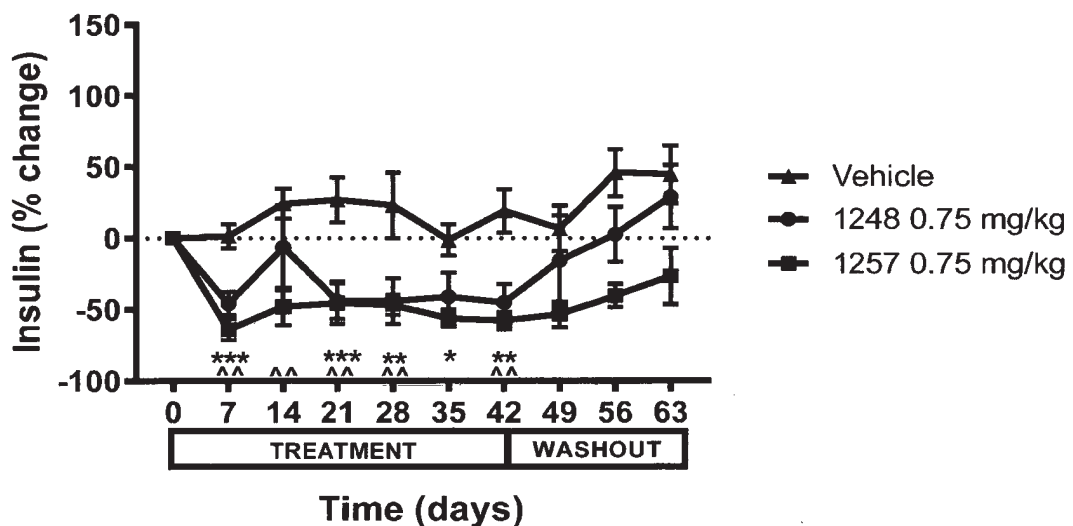
ANCOVA; *** $p < 0.001$ vs vehicle for 1248 0.75 mg/kg; ^^ $p < 0.001$ vs vehicle for 1257 0.75 mg/kg Data represented as group mean $\pm$ SEM; $n = 7-10/\text{group}$

FIG. 18



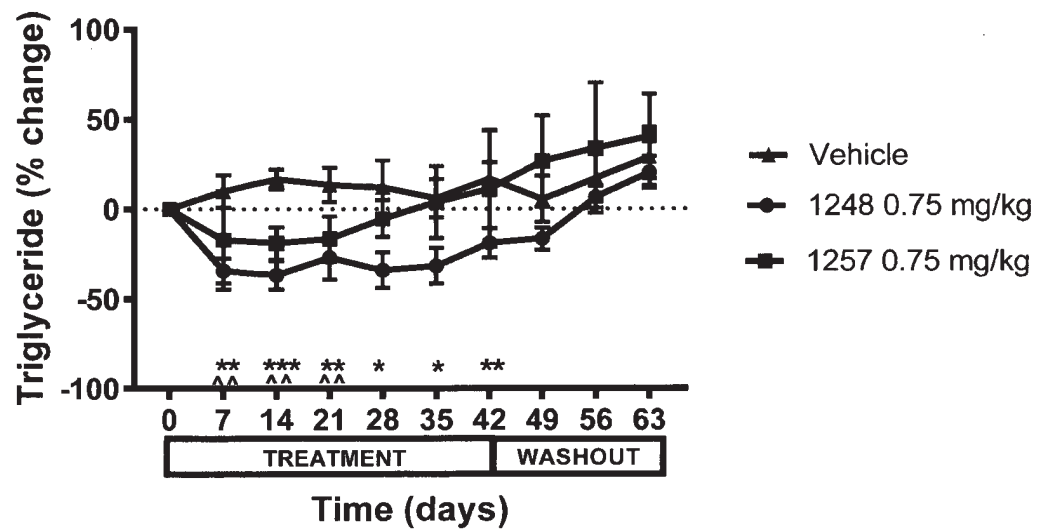
ANCOVA; *** $p < 0.001$ vs vehicle for 1248 0.75 mg/kg; ^^ $p < 0.001$ vs vehicle for 1257 0.75 mg/kg Data represented as group mean $\pm$ SEM; $n = 7-10$ /group

FIG. 19



ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehicle for 1248 0.75 mg/kg;
^^ $p < 0.01$ vs vehicle for 1257 0.75 mg/kg
Data represented as group mean $\pm$ SEM; $n = 7-10$ /group

FIG. 20

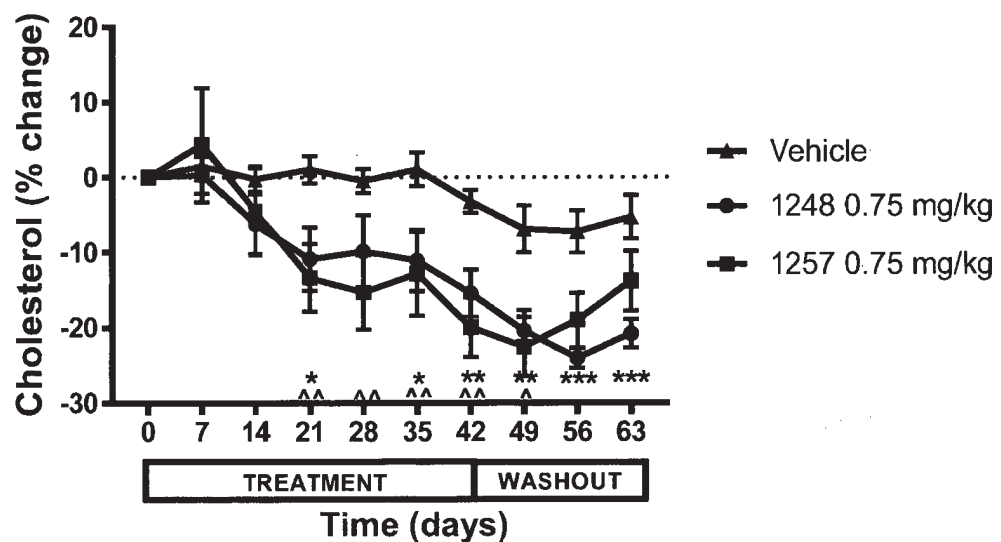


ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehicle for 1248 0.75 mg/kg;

^^ $p < 0.01$ vs vehicle for 1257 0.75 mg/kg

Data represented as group mean $\pm$ SEM; $n = 7-10$ /group

FIG. 21

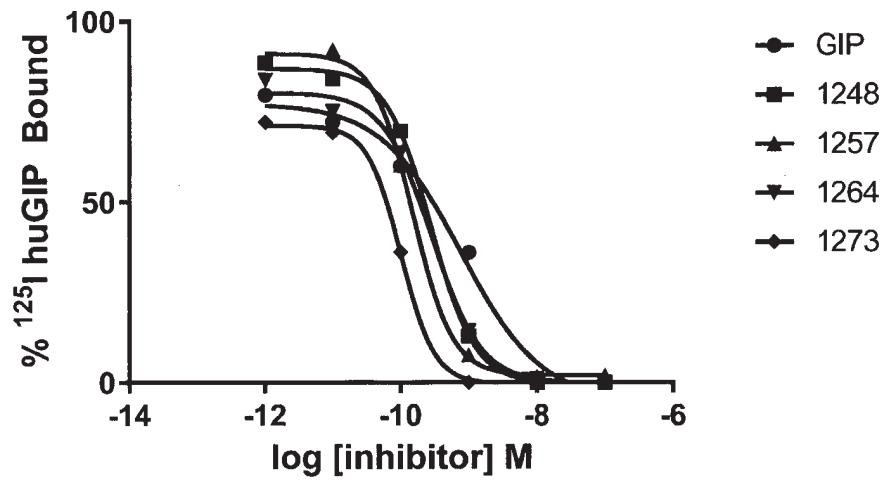


ANCOVA; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs vehicle for 1248 0.75 mg/kg; ^ $p < 0.05$,

^^ $p < 0.01$ vs vehicle for 1257 0.75 mg/kg

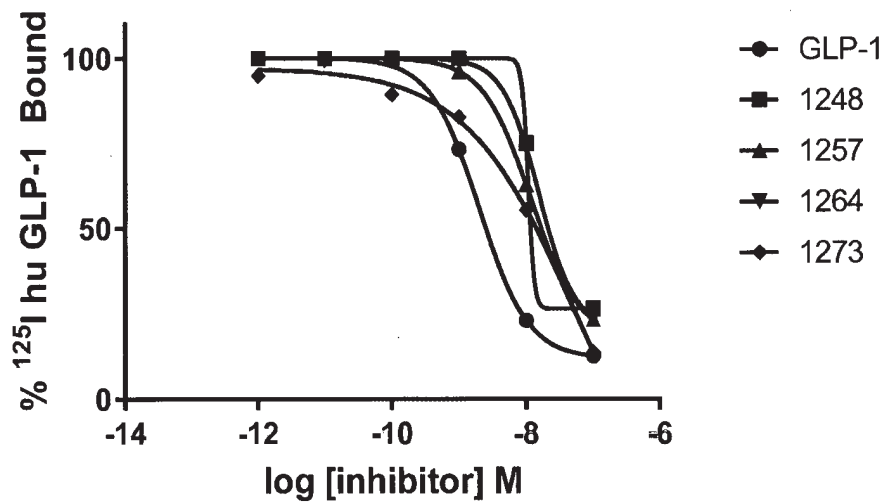
Data represented as group mean $\pm$ SEM; $n = 7-10$ /group

FIG. 22A

¹²⁵I huGIP Radioligand Binding Assay

	GIP	1248	1257	1264	1273
IC ₅₀	7.788e-010	2.806e-010	1.539e-010	2.928e-010	1.021e-010

FIG. 22B

¹²⁵I huGLP-1 Radioligand Binding Assay

	GLP-1	1248	1257	1264	1273
IC ₅₀	1.995e-009	1.069e-008	1.174e-008	1.548e-008	5.627e-008

FIG. 23

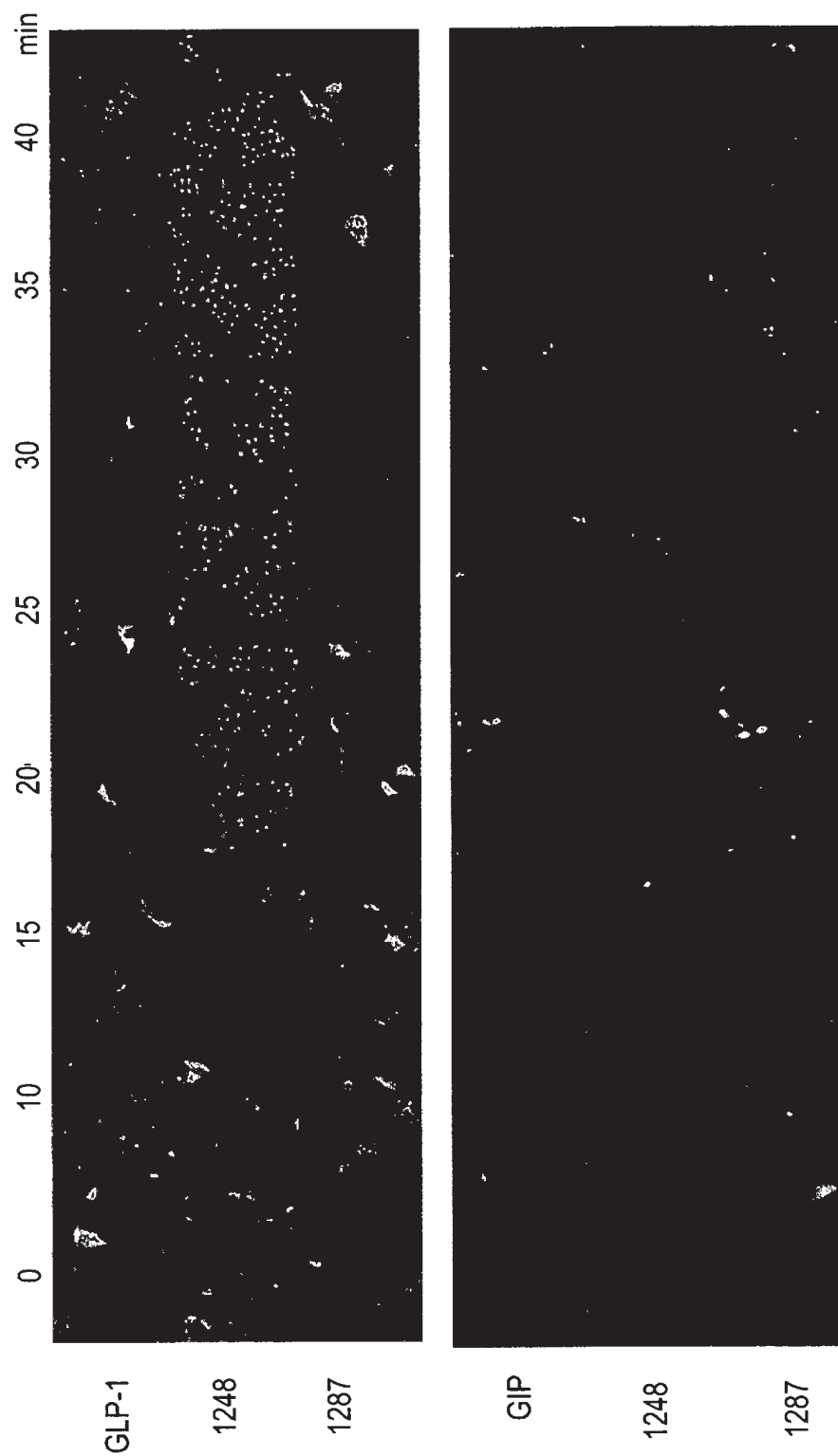


FIG. 24A

GLP1R Internalization in CHOK1 GIPR/GLP-1R M1 cells

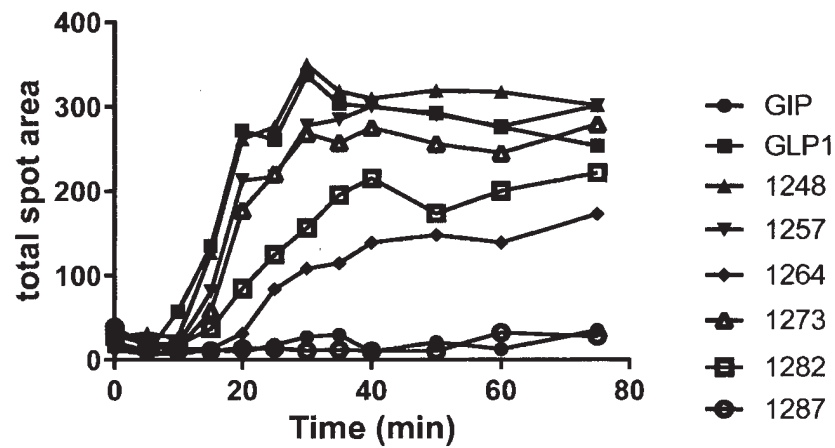
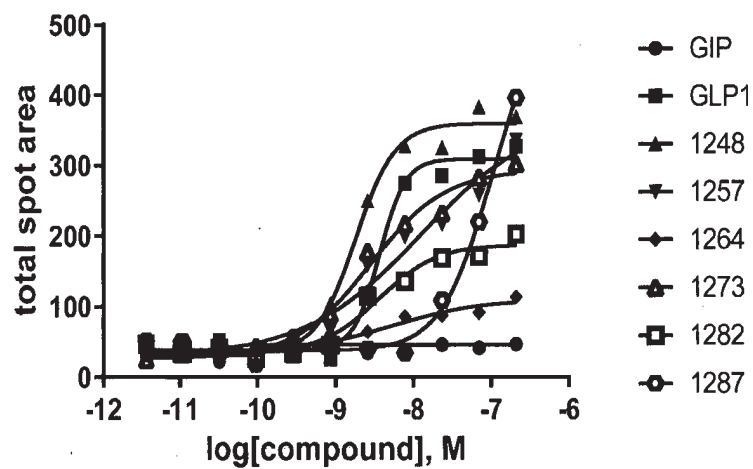


FIG. 24B

GLP-1R Internalization in CHOK1 GIPR/GLP-1R M1 cells



	GIP	GLP1	1248	1257	1264	1273	1282	1287
EC50	~ 9.480e-011	3.689e-009	1.834e-009	1.235e-008	5.348e-009	2.830e-009	3.606e-009	1.033e-007

FIG. 25A



FIG. 25B

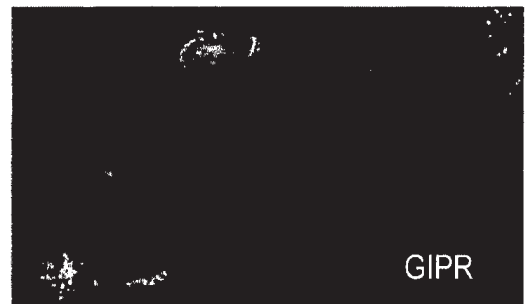


FIG. 25C

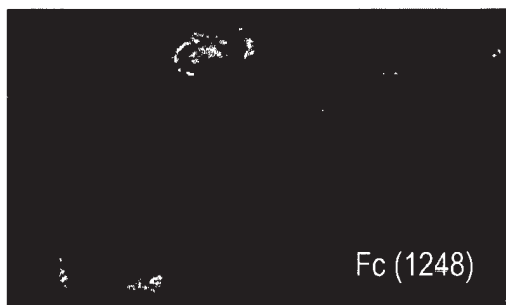


FIG. 25D



FIG. 26A

Effects of inhibition of receptor internalization on
1248 induced cAMP activity

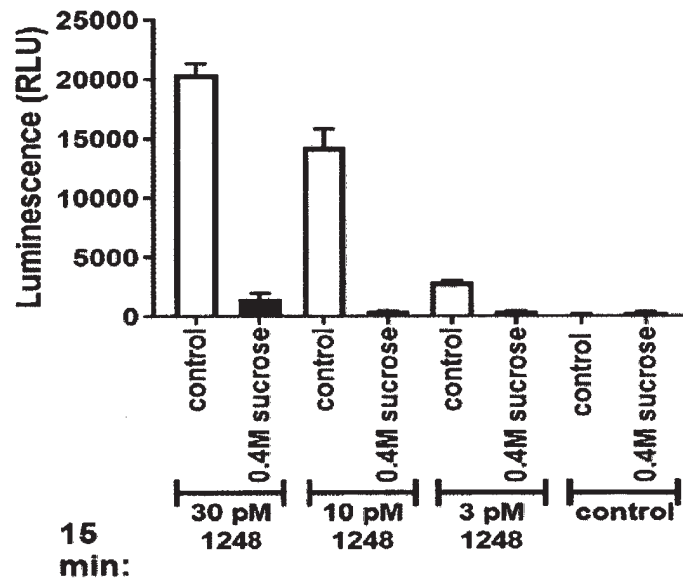


FIG. 26B

GloSensor cAMP assay
1248

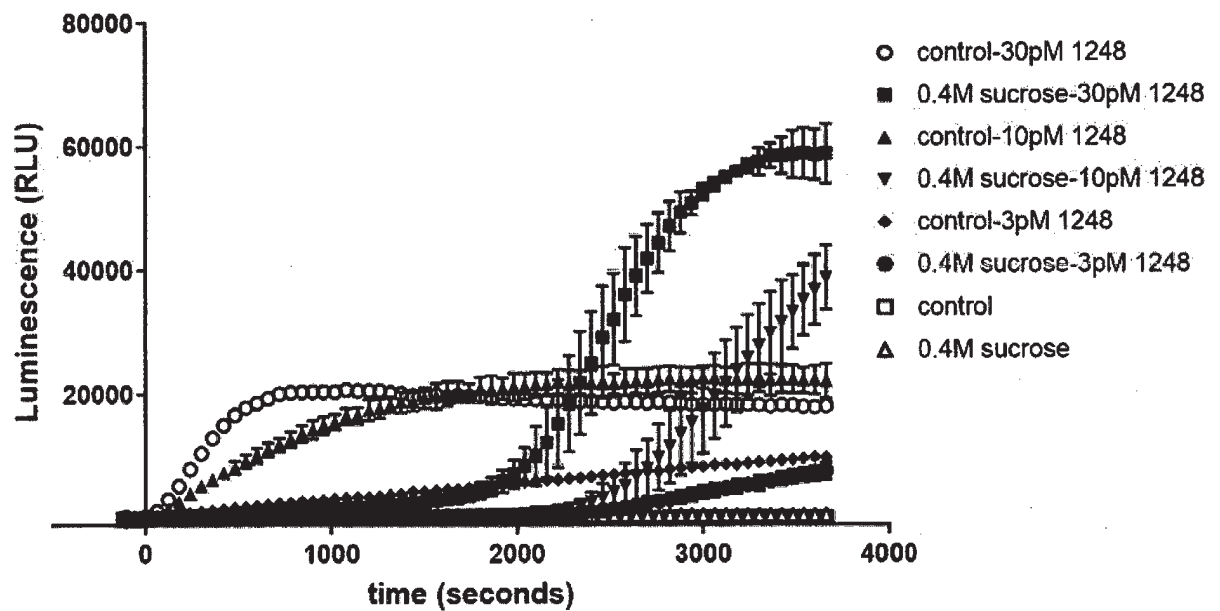


FIG. 27A

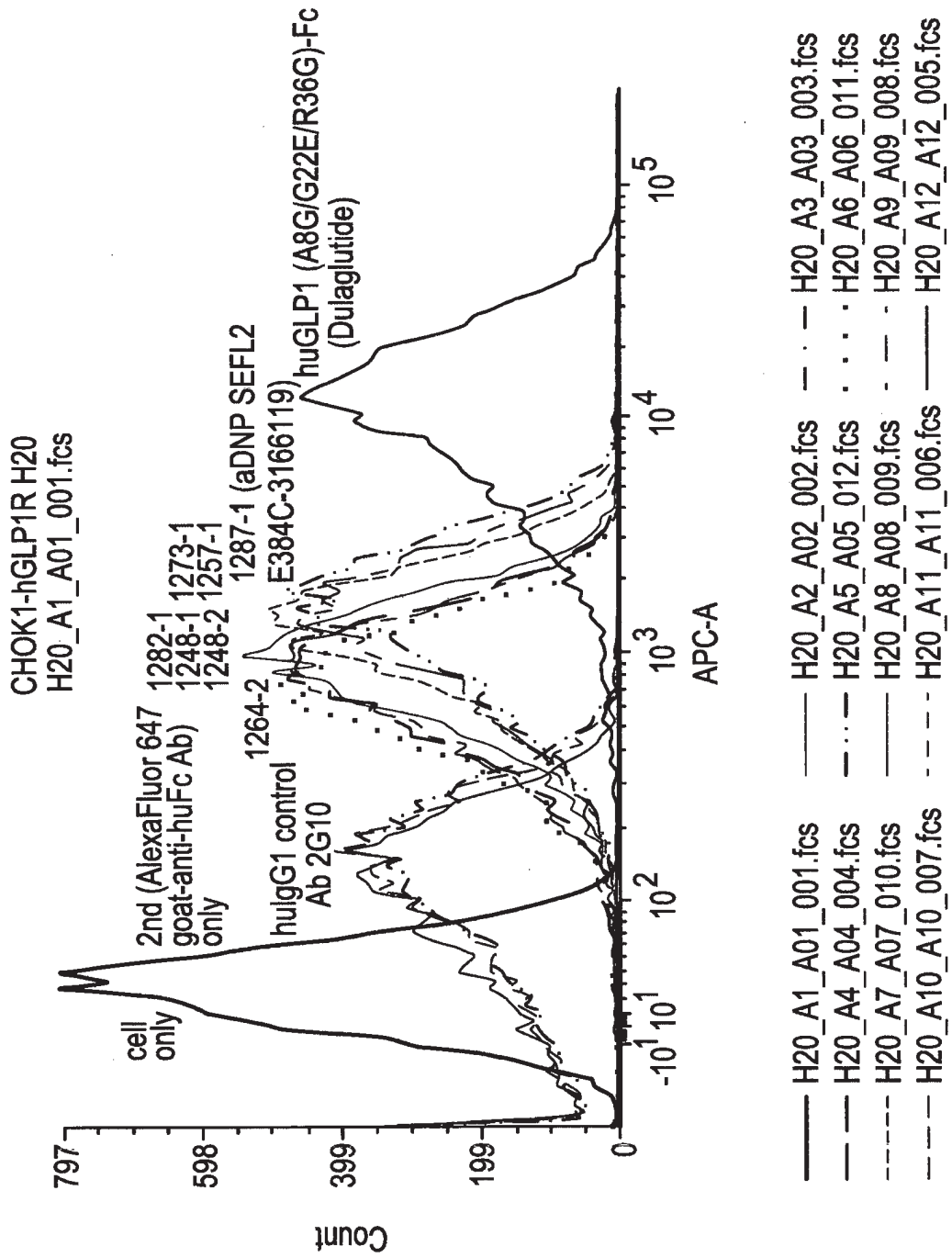


FIG. 27B

293T-GIPR clone 10

M1_A1_A01_001.fcs

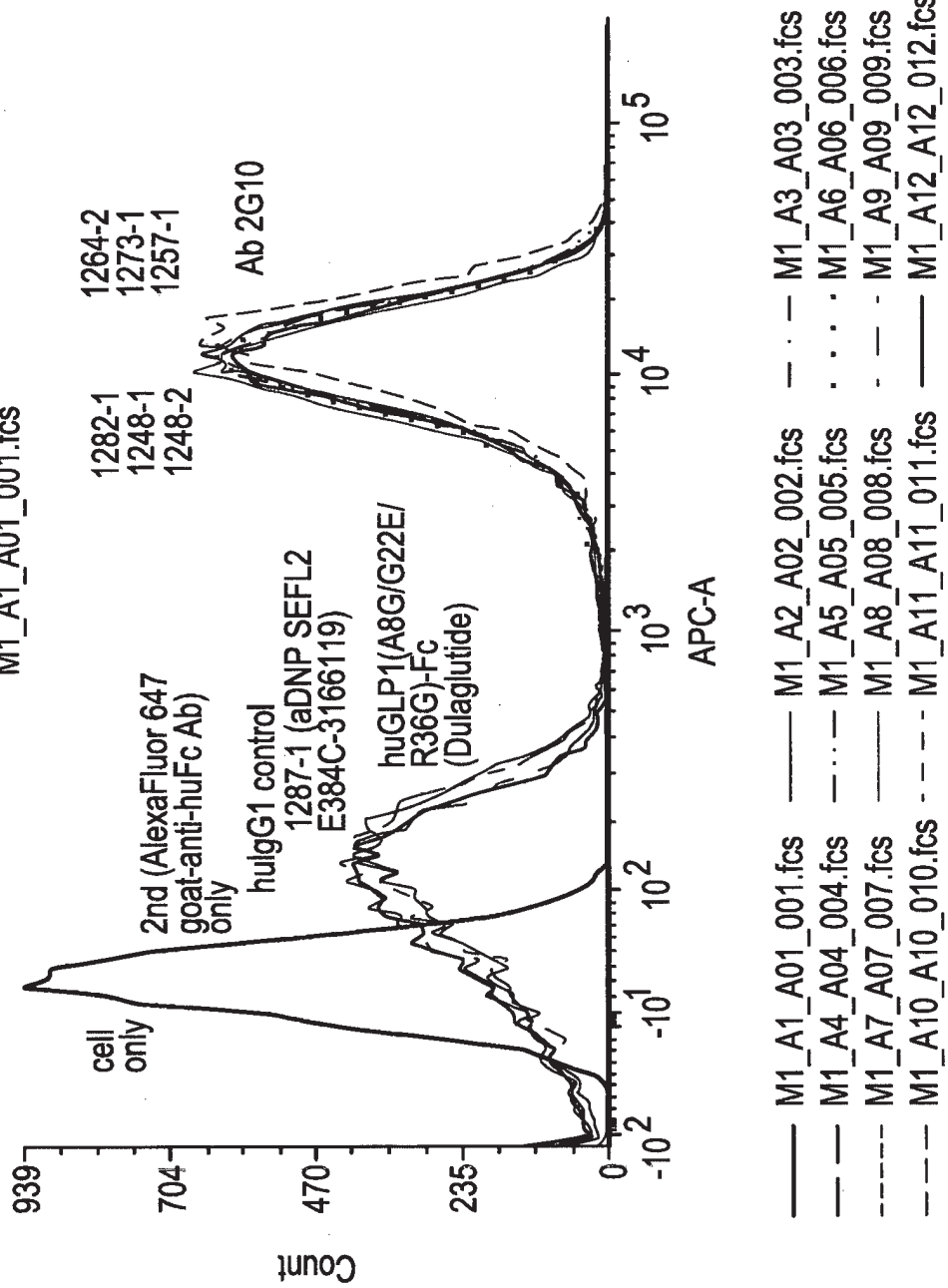
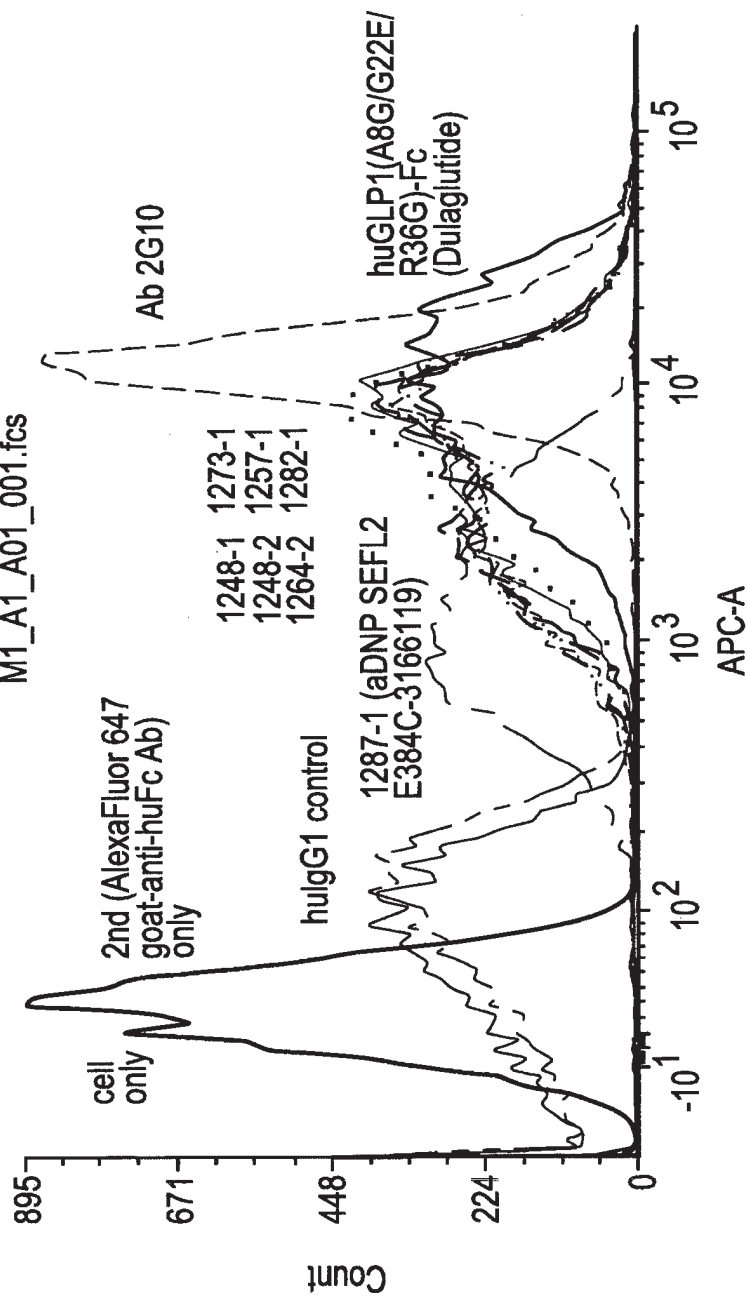


FIG. 27C

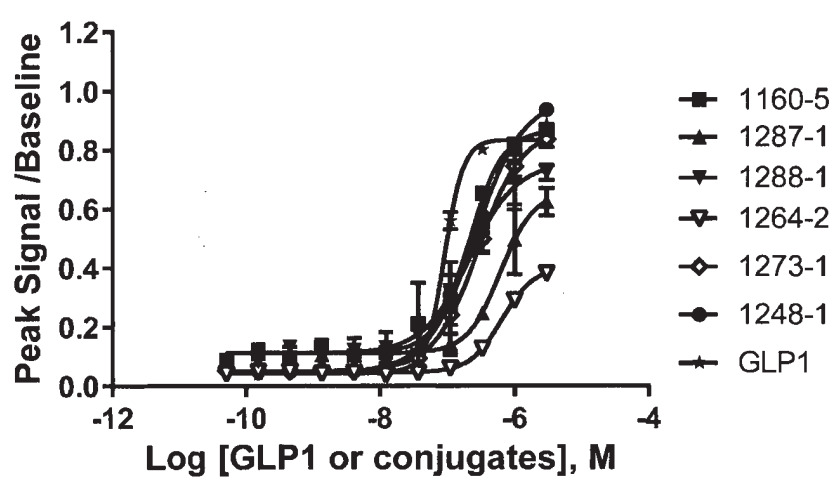
CHOK1-hGLP1R/hGIPR M1
M1_A1_A01_001.fcs



— M1_A1_A01_001.fcs — M1_A2_A02_002.fcs — M1_A3_A03_003.fcs
 - - M1_A4_A04_004.fcs - - M1_A5_A05_005.fcs - - M1_A6_A06_006.fcs
 . . . M1_A7_A07_007.fcs . . . M1_A8_A08_008.fcs . . . M1_A9_A09_009.fcs
 - - M1_A10_A10_010.fcs - - M1_A11_A11_011.fcs — M1_A12_A12_012.fcs

FIG. 28

Calcium Flux assay in ChoK1 GLP1R/GIPR M1 cells



	1160-5	1287-1	1288-1	1264-2	1273-1	1248-1	GLP1
EC50	2.098e-007	6.152e-007	2.141e-007	6.485e-007	2.862e-007	2.594e-007	9.123e-008

FIG. 29A

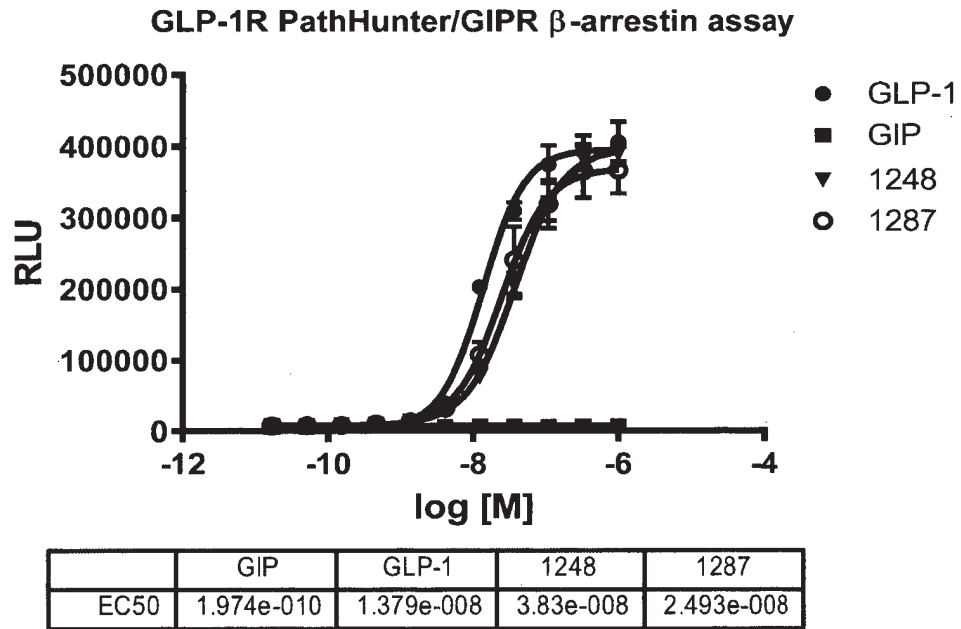


FIG. 29B

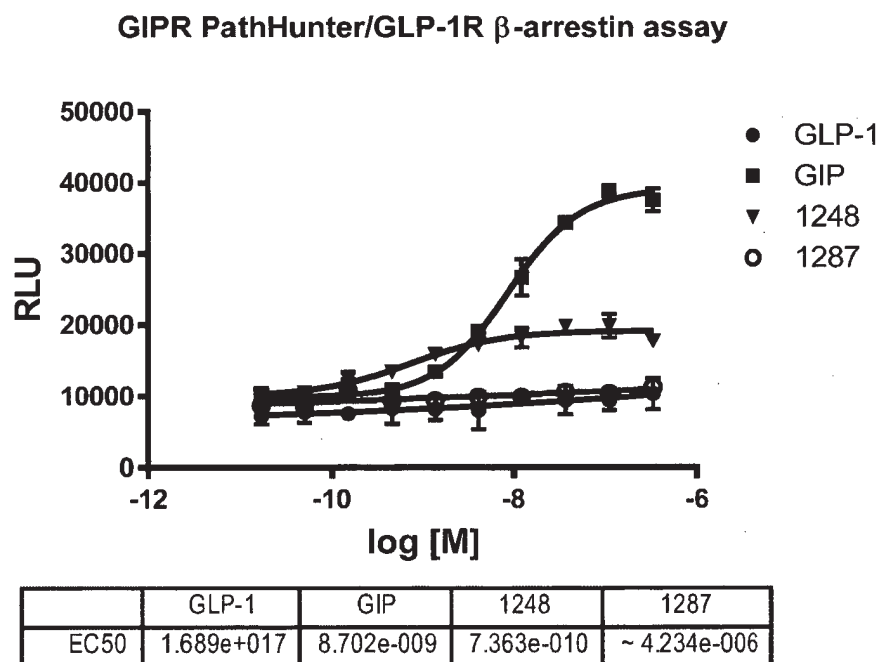


FIG. 30

**Glucose-stimulated insulin secretion assay:
low and high glucose conditions in
human pancreatic microislets**

