



Discover Positive Allosteric Modulators of GLP-1R for treatment of obesity and diabetes

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Where healthcare and science converge.

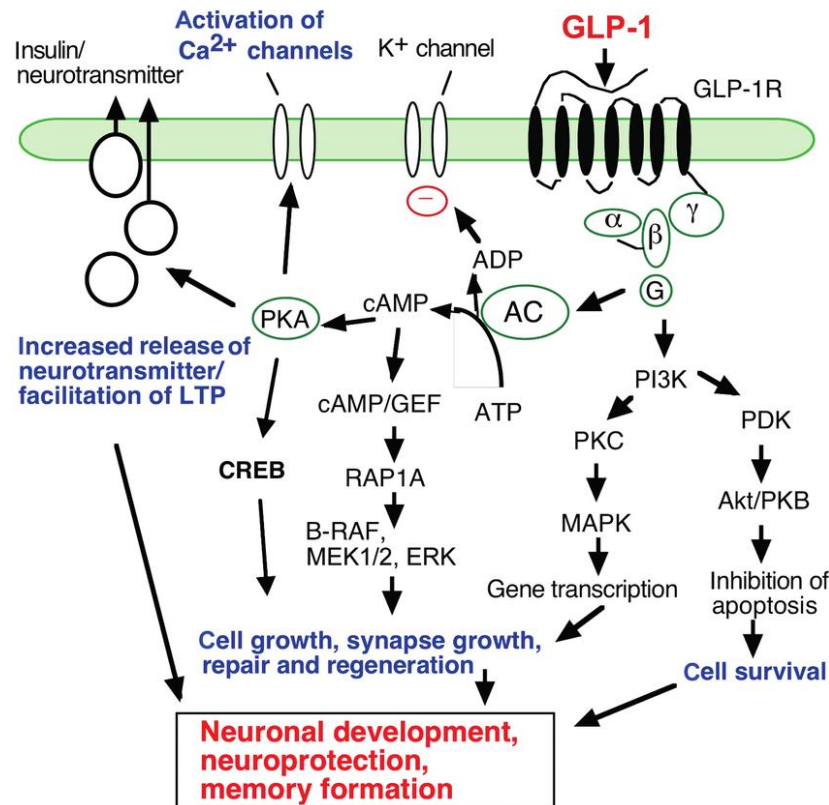


Diabetes is a serious health threat

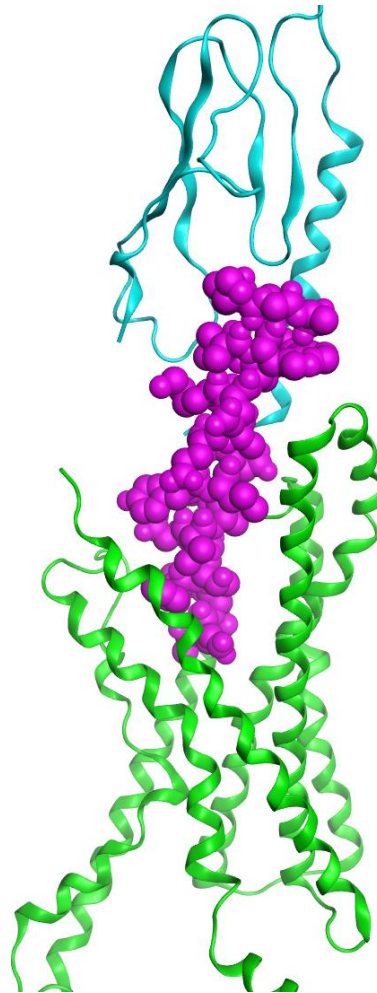
- 30.3 million people have diabetes (9.4% of the US population)
- 84.1 million adults aged 18 years or older have prediabetes (33.9% of the US population)

GLP-1 receptor (GLP-1R) is a target for treatment of type-2 diabetes

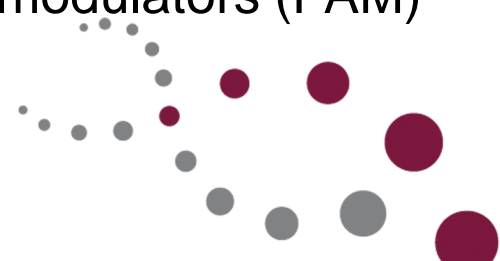
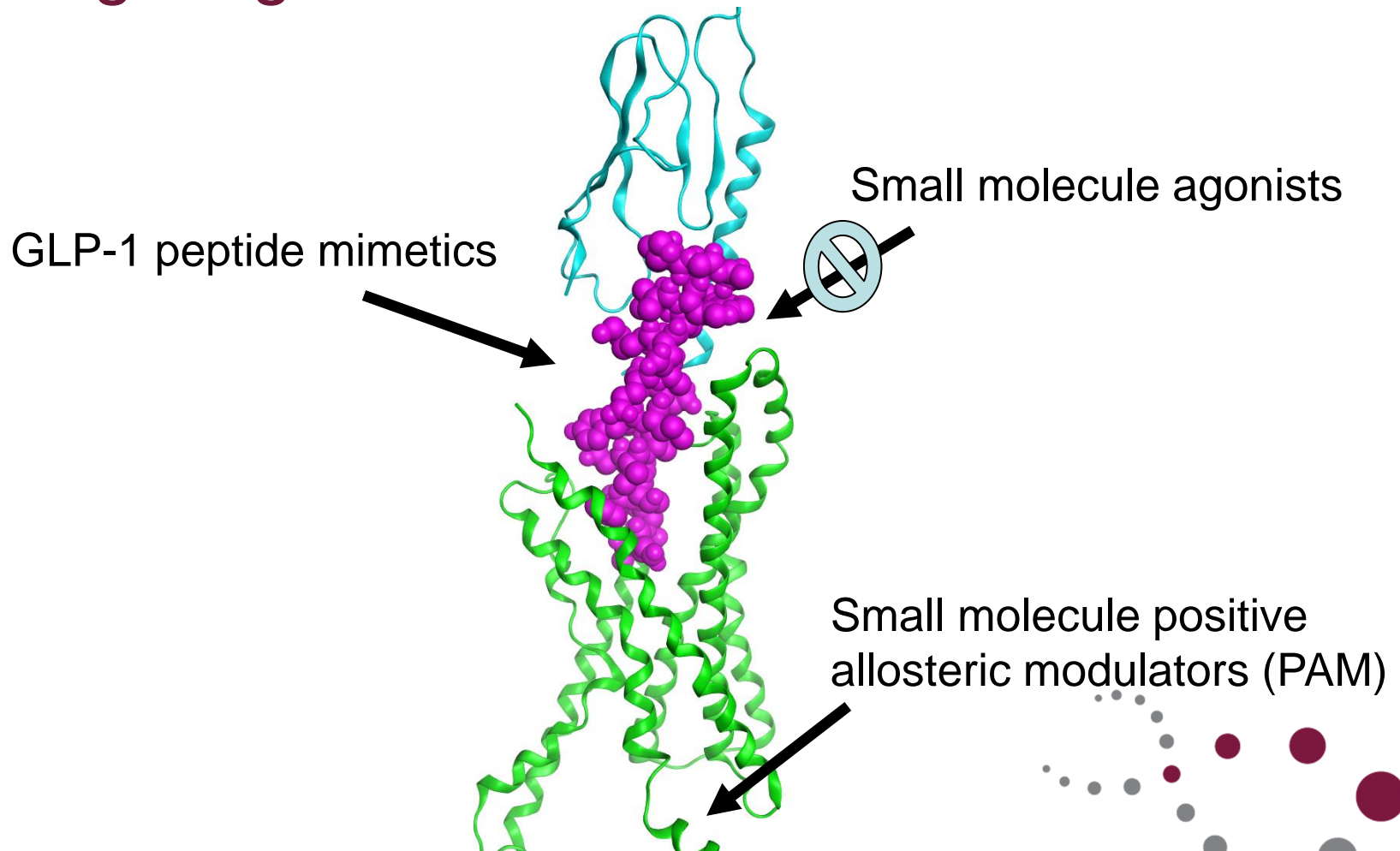
Pathways of GLP-1 receptor activation



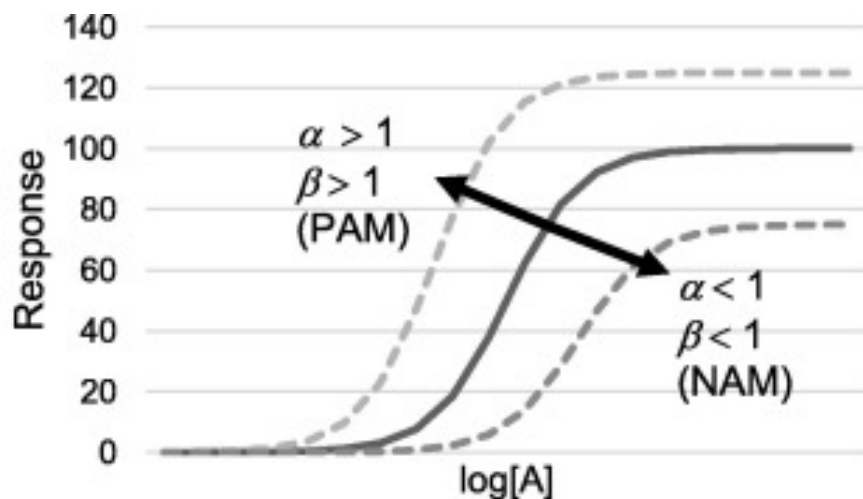
GLP-1R is a transmembrane protein



Current Approaches for Drug Discovery Targeting GLP-1R



Model of Allosteric Modulators



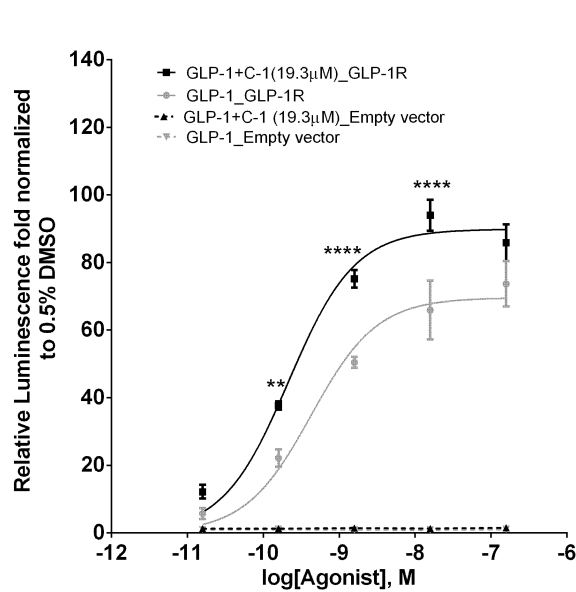
- Binding cooperativity (α)
- Efficacy cooperativity (β)

Our Structure-Based Approach: Compound C-1

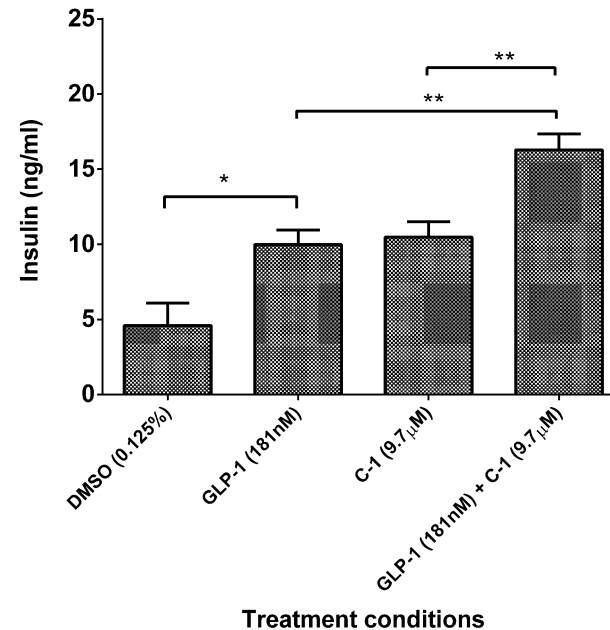
- Compound C-1 is commercially available
- Compound C-1 has Molecular Weight of 399



C-1 is a PAM of GLP-1R



Luciferase Activity

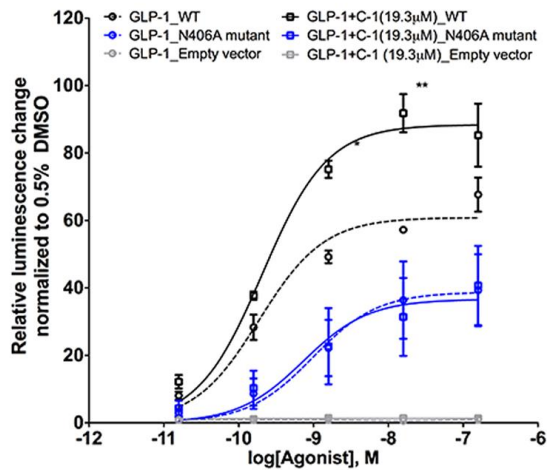


Insulin Secretion

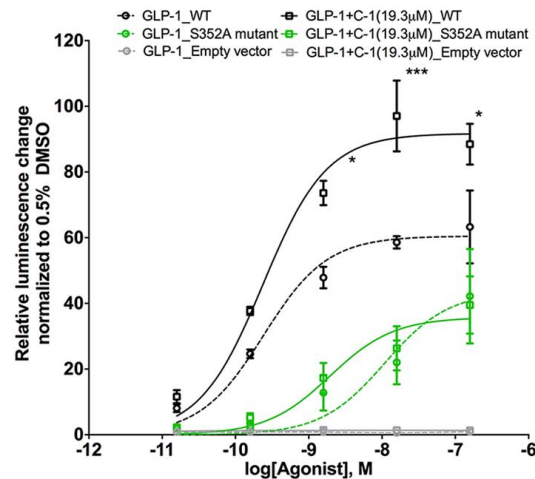
GLP-1 is used as a control in both experiments

Site-specific mutagenesis confirms the C-1 binding site

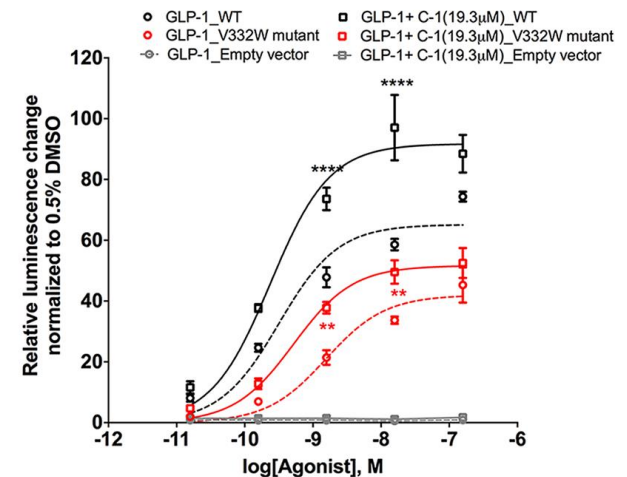
a



b



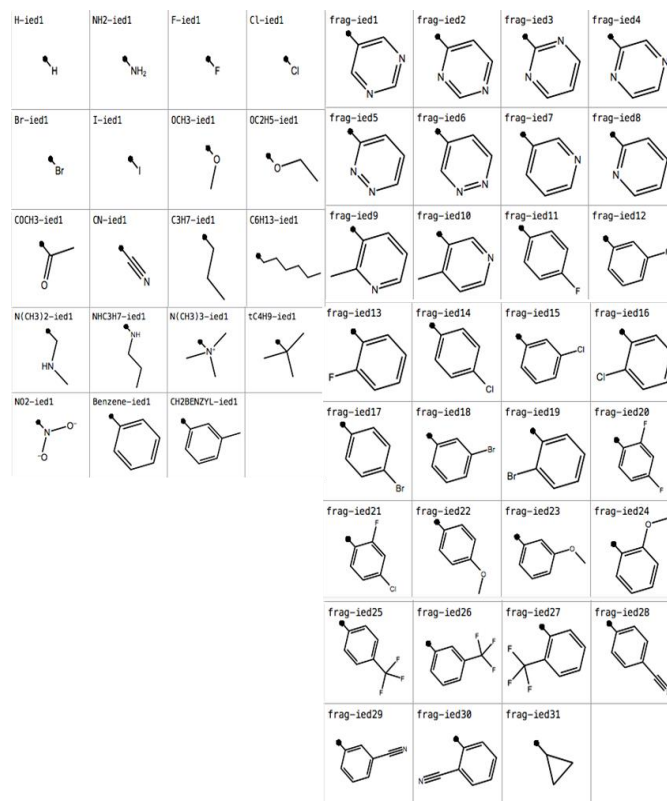
c



GLP-1 is used as a control in all experiments



Structure-Based *In Silico* Design

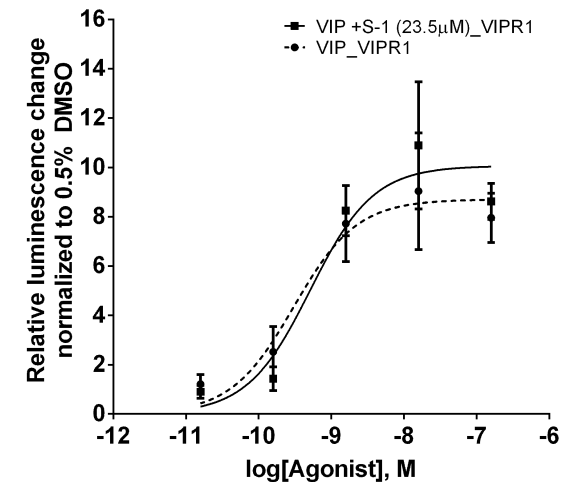
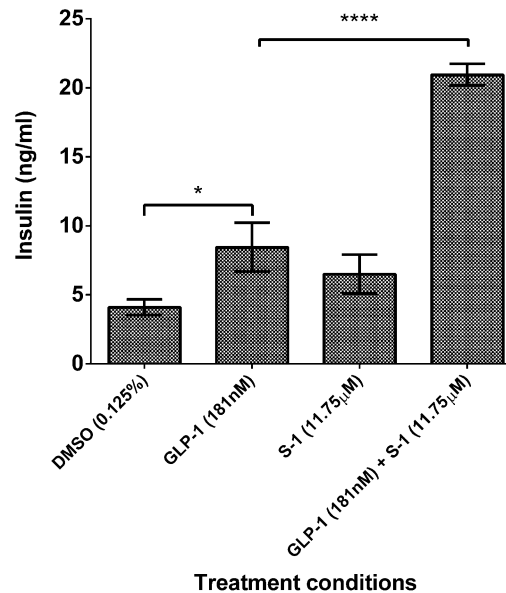
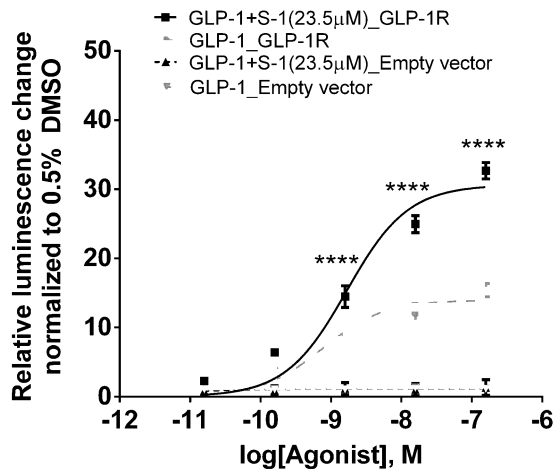


Chemical Synthesis of Designed Compounds: Compound S-1

- Compound S-1 is structurally related to C-1
- Compound S-1 is a novel compound



S-1 is another PAM of GLP-1R



Luciferase Activity

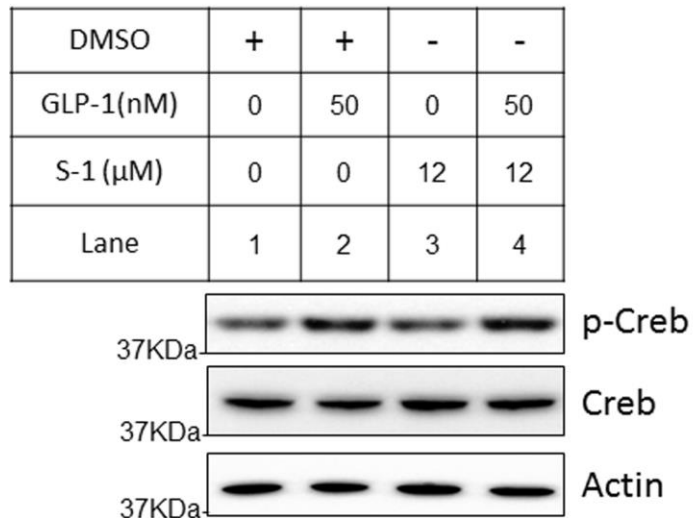
Insulin Secretion

Specificity vs. VIPR

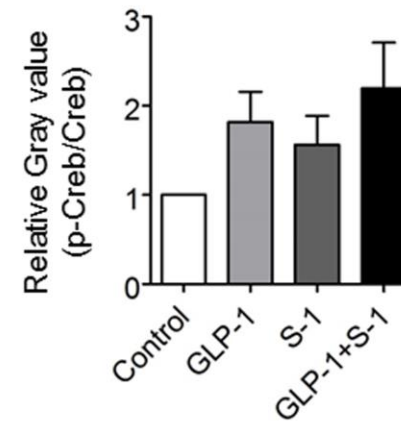
GLP-1 is used as a control in all experiments

S-1 Induced Signaling Pathway

A



B



S-1 is a great lead compound

- μM potency
- Specific to GLP-1R, not active to VIPR
- Lipinski's rule of five
- Smallest MW (239)

