Development of a G protein mimetic toolbox to conformationally lock G protein-coupled receptors (GPCRs) in the active state

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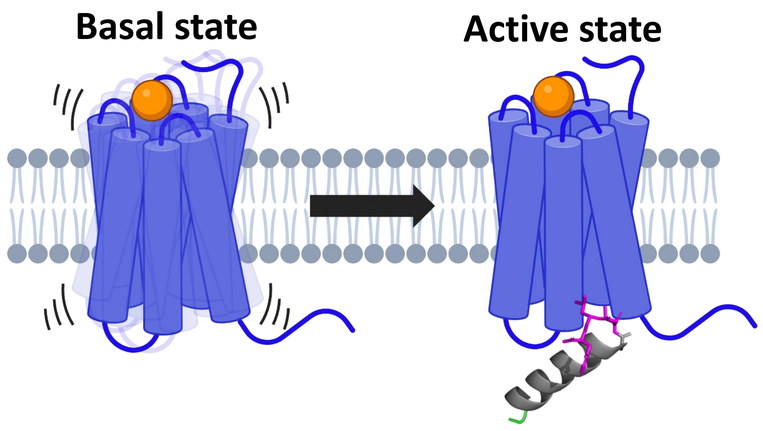
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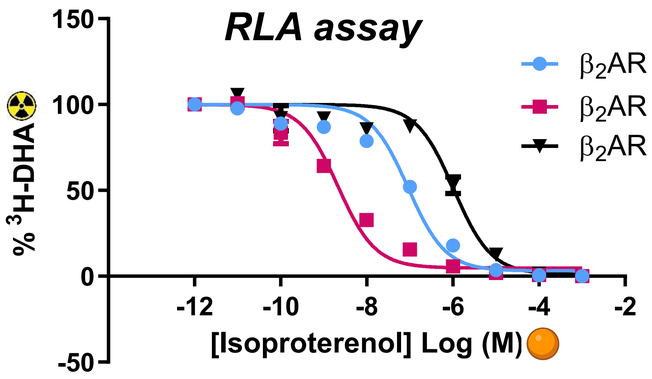
INTRODUCTION

G protein-coupled receptors (GPCRs) are membrane-spanning proteins and are targeted by over 30% of prescribed drugs on the market. Despite their central role in modern medicine, they are therapeutically underexplored because of their intrinsic dynamic behavior, which makes them difficult to study. Stabilizing defined receptor states has therefore become essential for functional and structural investigations.[1] Our group is developing generic **G protein-mimicking peptides** capable of **locking GPCRs in their active signaling state**.[2-5] The optimized G protein mimetics are **generic** and successfully lock several **Gαs-** & **Gαq-controlled GPCRs** in their active signaling state (β2AR, D1R, GHSR & M1R). Our tool compounds were proven useful in **reverse pharmacology screening** approaches (β2AR, D1R) and in examining GPCR signaling (GHSR).

OBJECTIVE

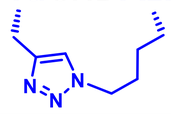


ALLOSTERIC STABILIZATION



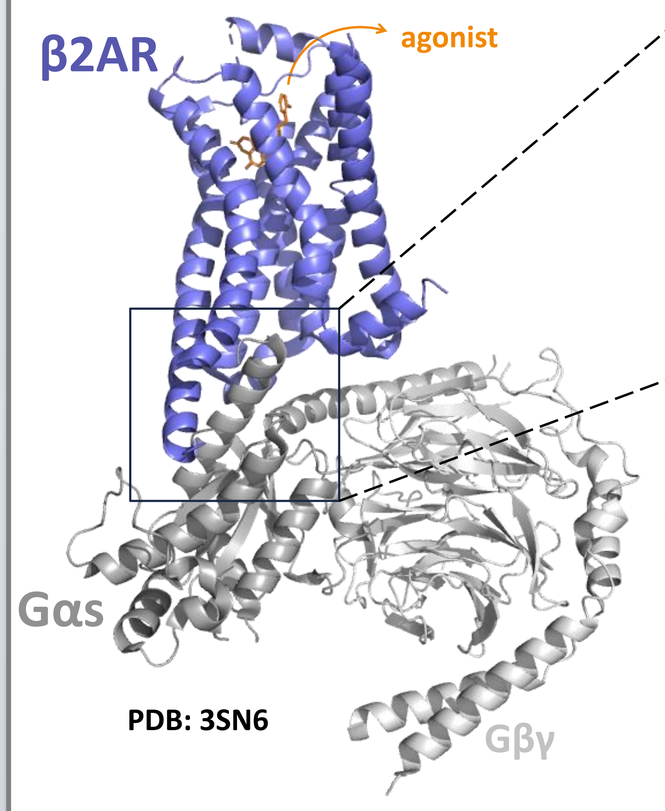
SBL-CM-51

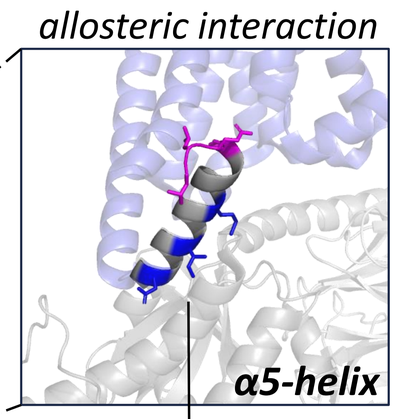
Ac-**KKK**FN**Pra**CRD**Azk**IQRMHLRQYE**Cha**L-OH

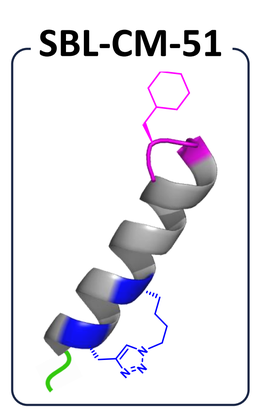


→ Also locks **D1R**

Gαs PEPTIDOMIMETIC DESIGN



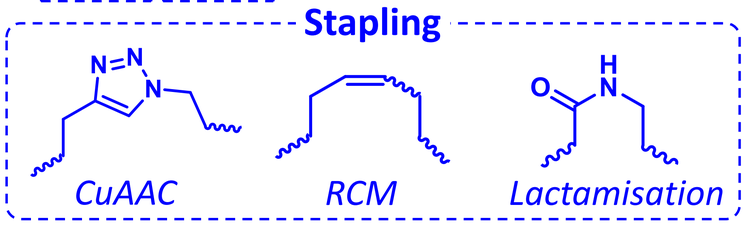




Point modifications

Ac-KKK-FN**D**CRD**I**IQR**M**HLRQ**YELL**-OH

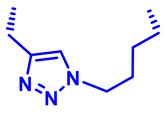
Stapling



Other G protein subfamilies? [3, 5]

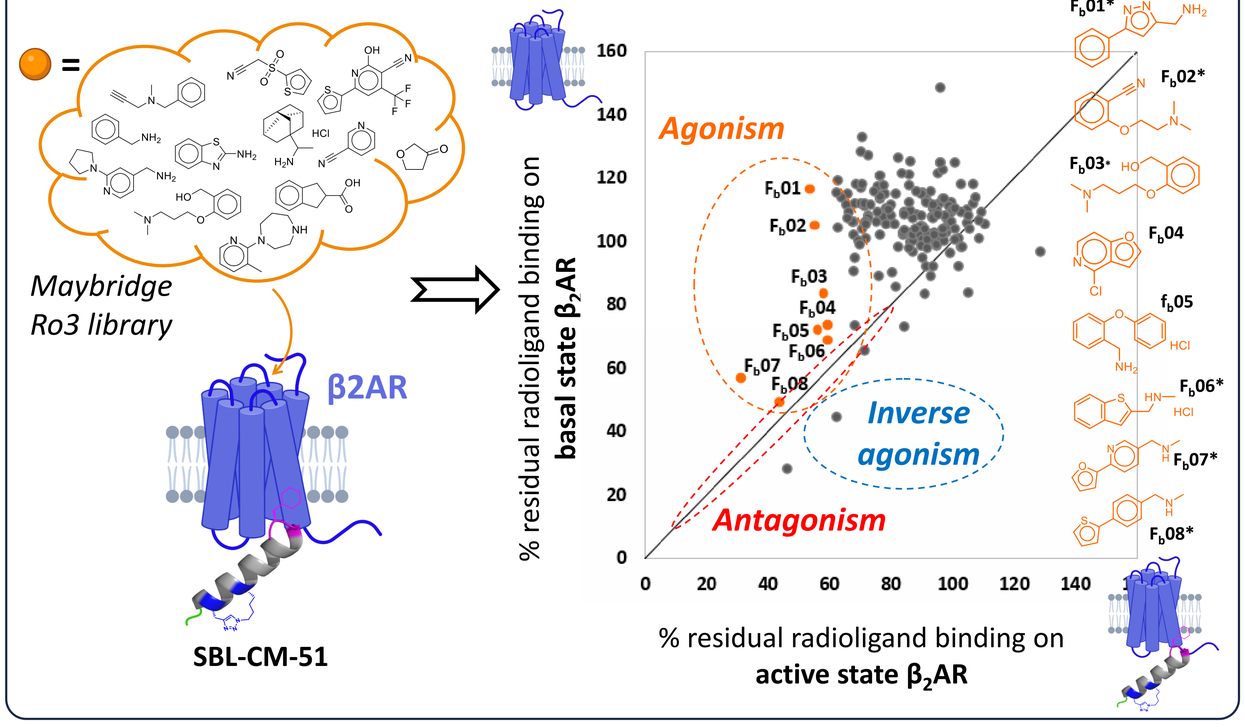
SBL-Gq-05

Ac-**KKK**FA**[Pra**VKD**Azk]**ILQLNLKEYNLV-OH ⟶ Locks the Gq-controlled Ghrelin- **(GHSR)** & Muscarinic-1- **(M1R)** receptor in the active state

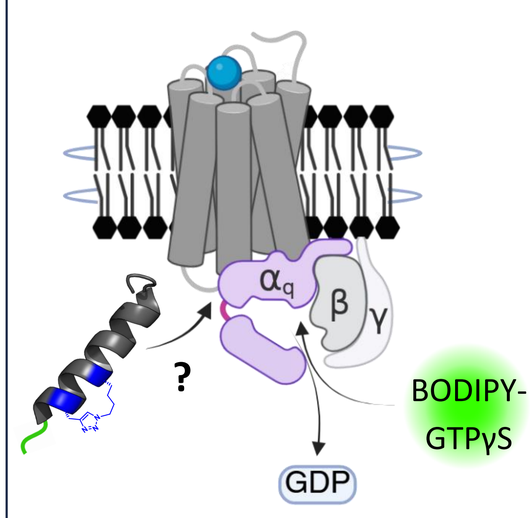


APPLICATIONS

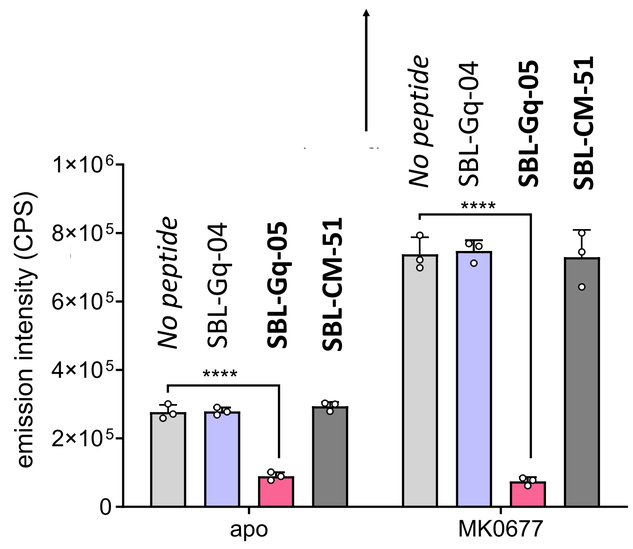
Fragment-based drug screens [2]



GPCR signaling studies [3]

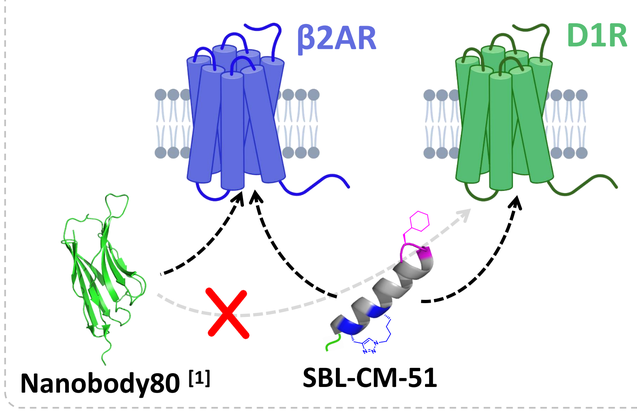


***SBL-Gq-05 competes** with Gq protein binding, while SBL-CM-51 does not*

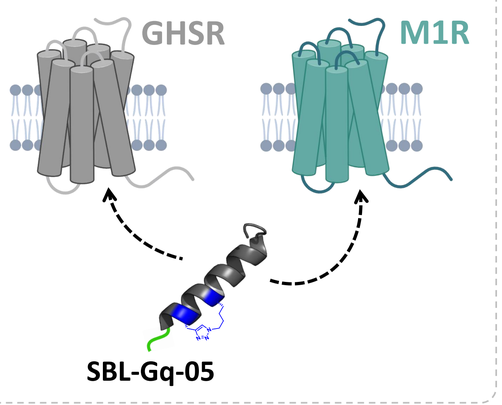


GENERICITY OF THE TOOLS

Gs-controlled GPCRs [2, 4]



Gq-controlled GPCRs [3, 5]



CONCLUSIONS & PERSPECTIVES

SBL-CM-51 stabilizes **Gs**-controlled GPCRs in the active state

SBL-Gq-05 stabilizes **Gq**-controlled GPCRs in the active state

→ **Tool compounds** for use in **FBDS, GPCR signalling studies,…**

Acknowledgments

1SA8226N & OZR3939

SRP95

References

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[2] M. Mannes, *Angew. Chem. Int. Ed.* **2021**, *60*, 10247
[3] M. Mannes, *Sci. Signal.* **2025**, *18*, 7692
[4] M. Mannes, WO/2022/129630
[5] M. Mannes, WO/2023/247717