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A potential blueprint for the design of biased ligands for aminergic GPCRs

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A potential blueprint for the design of biased ligands for aminergic GPCRs

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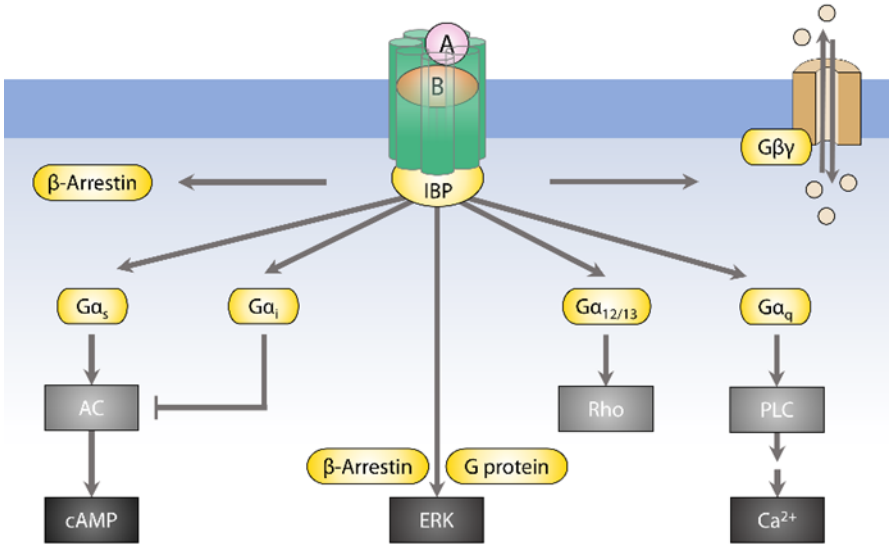
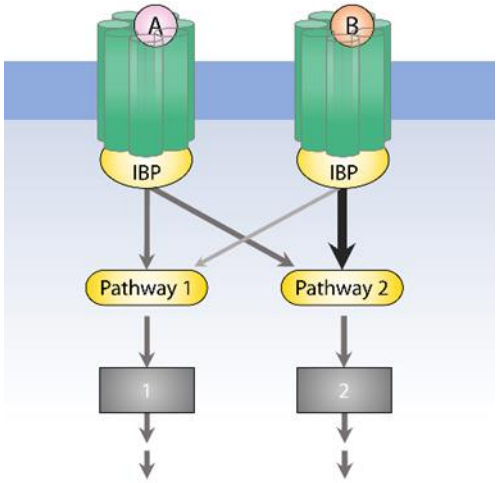
Abstract: GPCRs are omnipresent in the regulation of physiological processes and therefore account for the most prominent drug target class. However, nearly all drugs targeting GPCRs have been developed by the concept of receptors as simple on-off switches. This is surprising, because specifically addressing a distinct intracellular signaling pathway holds the potential to develop safer and more efficient drugs. In recent years more and more ligands have been reported that shift the naturally imprinted preference of a receptor's signaling profile, so-called biased ligands. It has been demonstrated for several aminergic GPCRs that an extension of their molecular structure towards extracellular receptor regions results in biased signaling. The underlying mechanism is a specific interference with the allosteric coupling mechanism by which extra- and intracellular sides of the receptor are conformationally linked. We propose a potential blueprint for the design of biased ligands based on the concept of specific interference with the extracellular receptor region and a restriction of its conformational space by extended ligand structures. While this design concept will likely identify new biased ligands, it remains a challenge to specifically design ligands with a desired signaling profile.
Keywords: GPCR; biased signaling, drug design, allosteric coupling

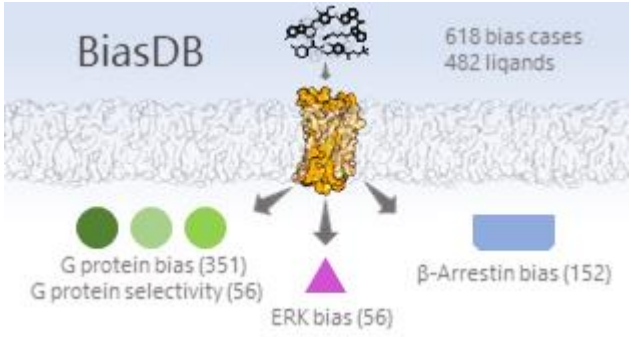
What is biased signaling





Ligand-dependent bias is a shift in the receptor‘s naturally imprinted preference for certain intracellular binding partners

BiasDB – a database for biased ligands



Data Search

Structure Search

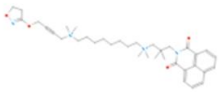
Visualize categories

SCAN ME

BiasDB: A Comprehensive Database for Biased GPCR Ligands, *BioRxiv*, first published August 24, 2019.

https://biasdb.drug-design.de/

Result for *iper-8-naph* as example query

Ligand	Structure	Receptor family	Receptor subtype	Bias category	Bias	Reference ligand	Assay one	Assay two	DOI
Iper-8-naph		Muscarinic receptor	M2 receptor	G protein	Gi / β-Arr	Acetylcholine	GTPγS	BRET	10.1038/ncomms2028
Iper-8-naph		Muscarinic receptor	M2 receptor	G protein selectivity	Gi / Gs	Iperoxo	GTPγS	cAMP	10.1021/acschembio.7b00275

Omieczynski ... and Bermudez; *BioRxiv*; **2019**

Detecting and quantifying biased signaling is far from being trivial

The major challenge for the BiasDB:
no standardized or commonly accepted
way how to report biased siganling

ERNEST
European Research
Network on Signal
Transduction | CA18133

BJP British Journal of Pharmacology

INVITED REVIEW | Open Access

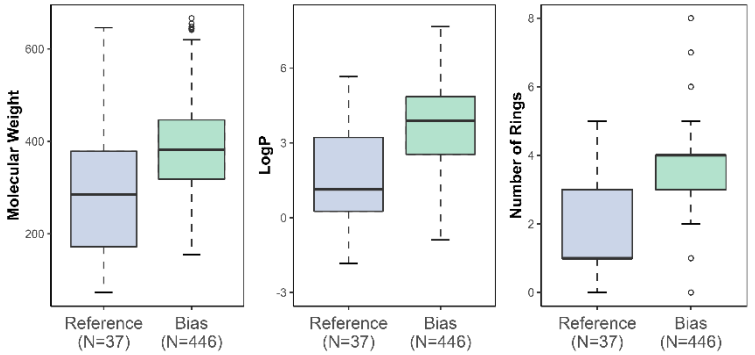
Community guidelines for GPCR ligand bias: IUPHAR review 32

Peter Kolb, Terry Kenakin, Stephen P. H. Alexander, Marcel Bermudez, Laura M. Bohn, Christian S. Breinholt, Michel Bouvier, Stephen J. Hill, Evi Kostenis, Kirill A. Martemyanov ... See all authors

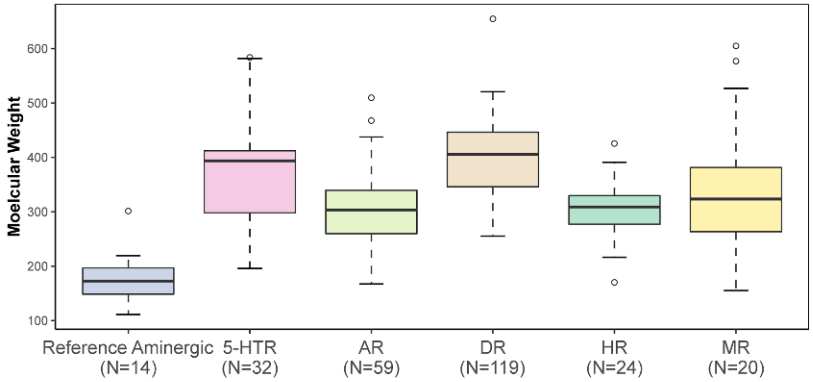
Kolb, Kenakin, Alexander, Bermudez et al.; *Brit. J. Pharmacol*; **2022**

BiasDB – a database for biased ligands

Biased ligands have a trend to be larger, more lipophilic and contain more rings

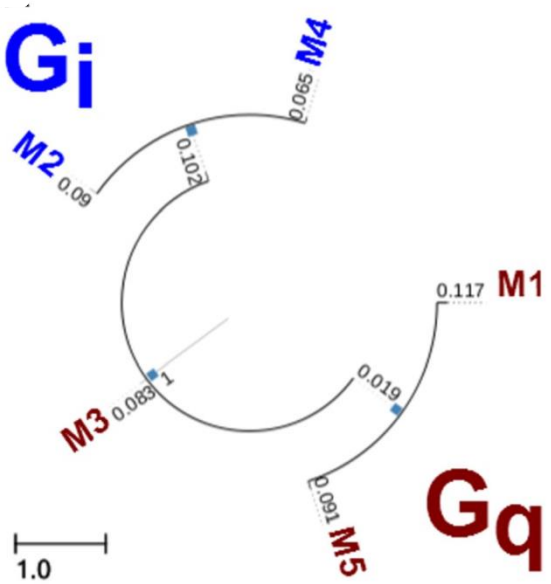


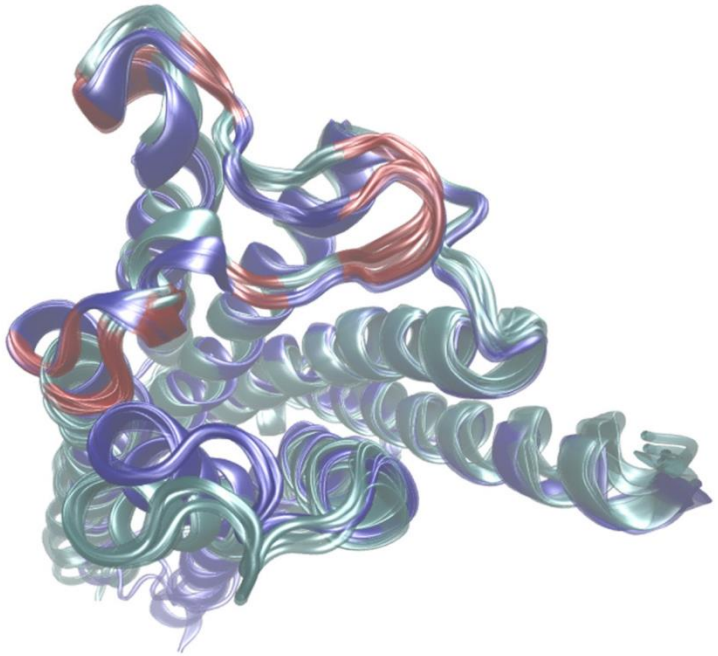
These trends are even more pronounced for aminergic GPCRs



Omieczynski ... and Bermudez; *BioRxiv*; **2019**

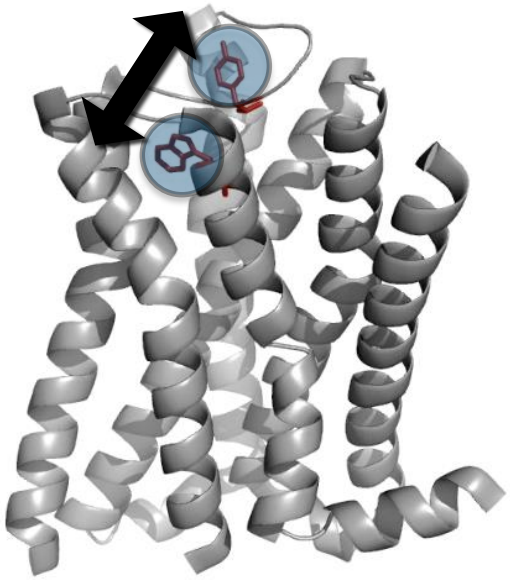
G protein selectivity



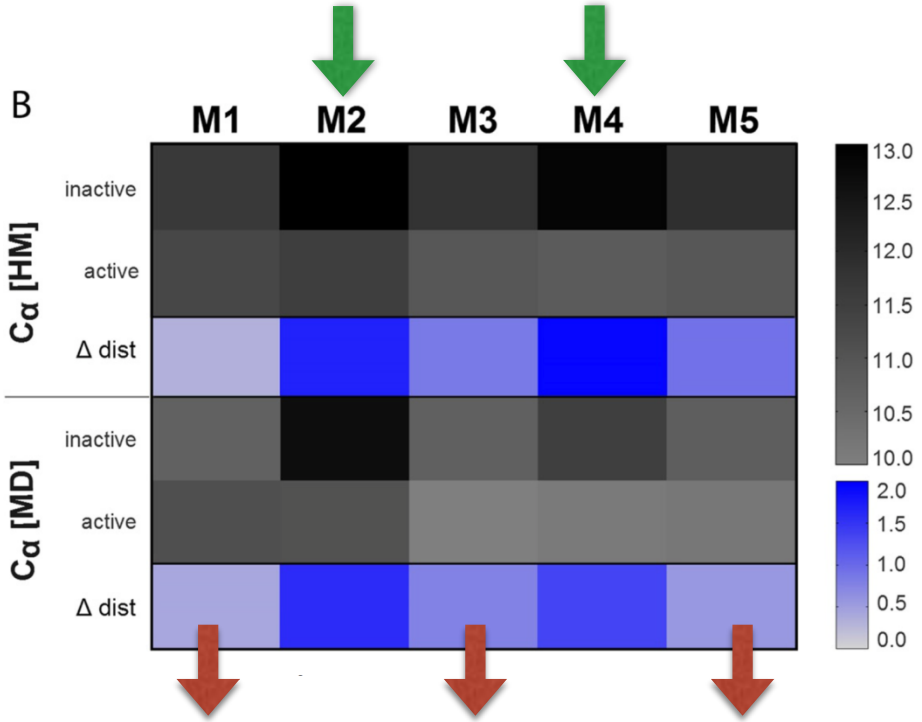


Bermudez et al., *Mol Inform*, **2015**

G protein selectivity



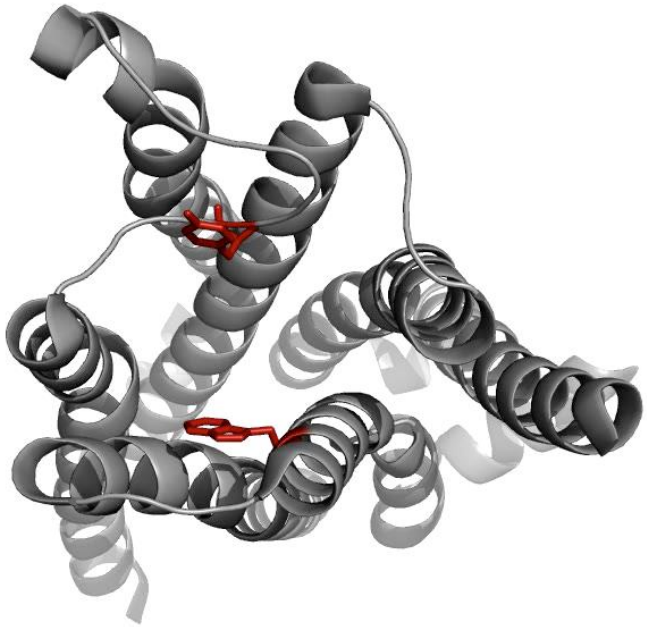
G_i coupling is linked to a large conformational ensemble

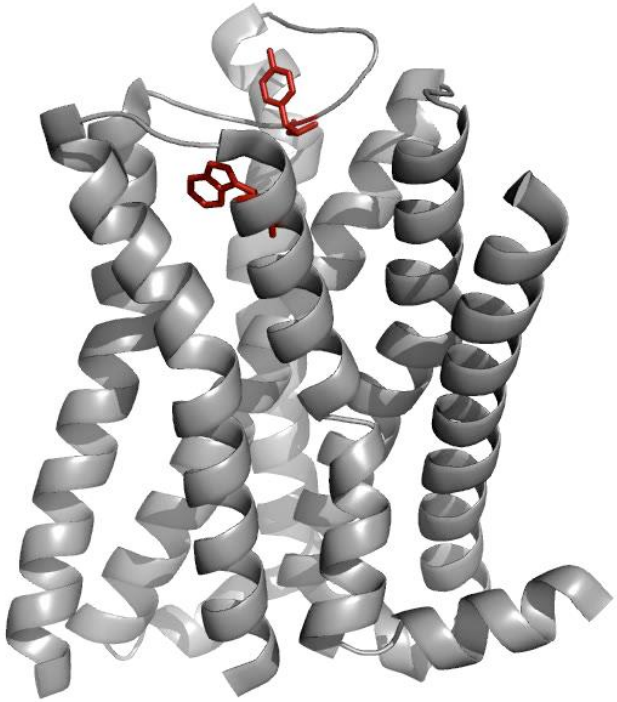


G_q coupling occurs within a more specific conformational space

Bermudez et al., *Mol Inform*, **2015**

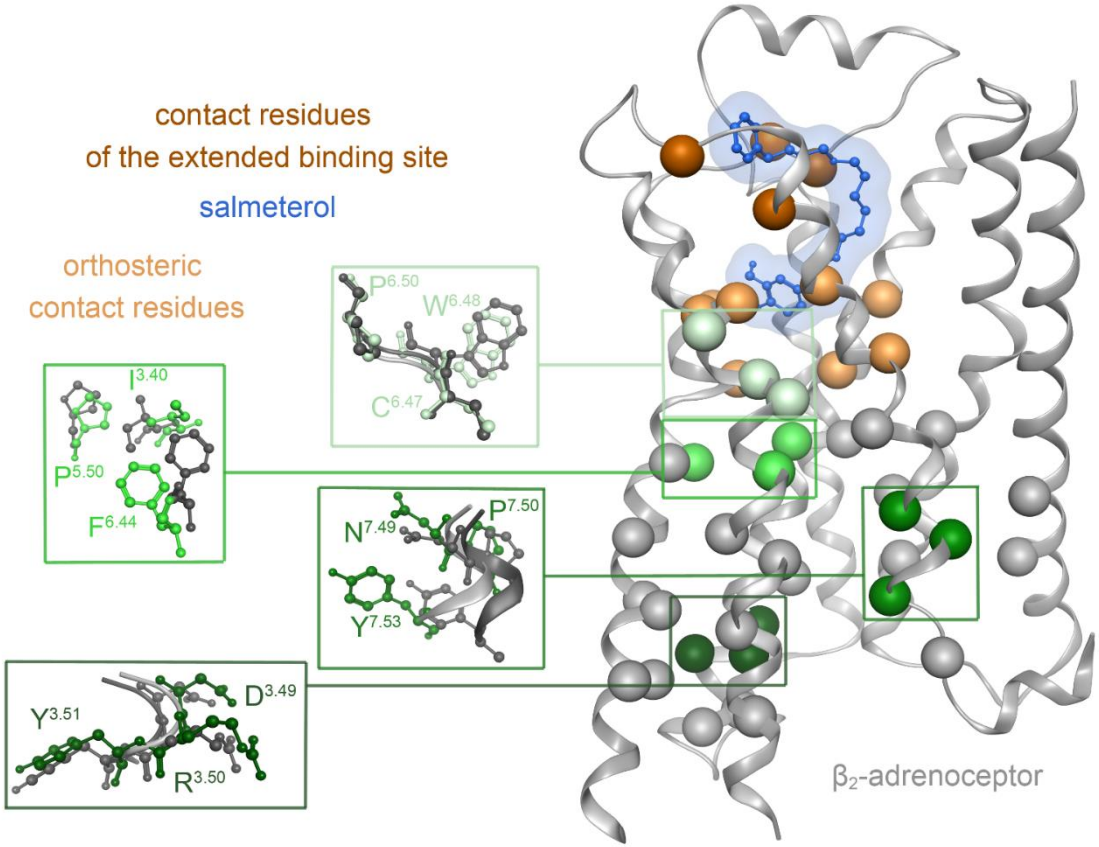
GPCR activation





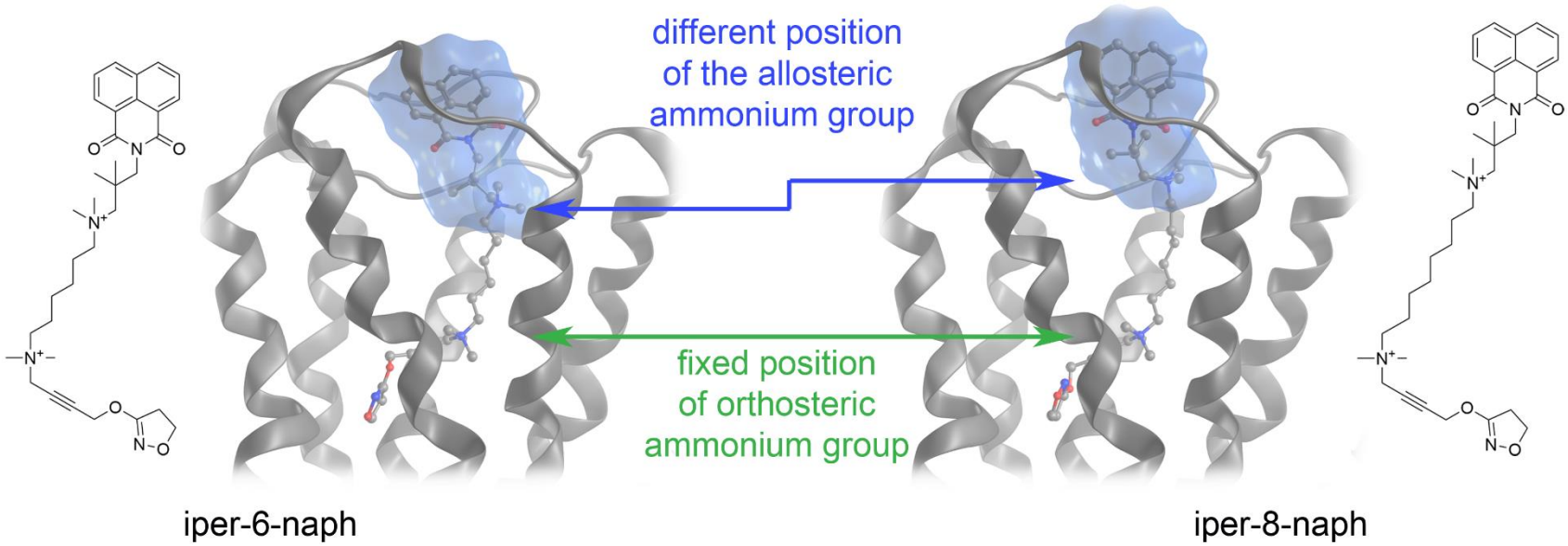
Bock and Bermudez et al., *J Biol Chem*, **2016;** Bermudez and Bock et al., *ACS Chem Biol*, **2017;** Holze and Bermudez et al., *ACS Pharmacol Transl Sci*, **2020;** Bock and Bermudez, *FEBS J*, **2021**

Allosteric coupling and GPCR activation



Bock and Bermudez, *FEBS J*, **2021**

G protein selectivity vs. biased signaling

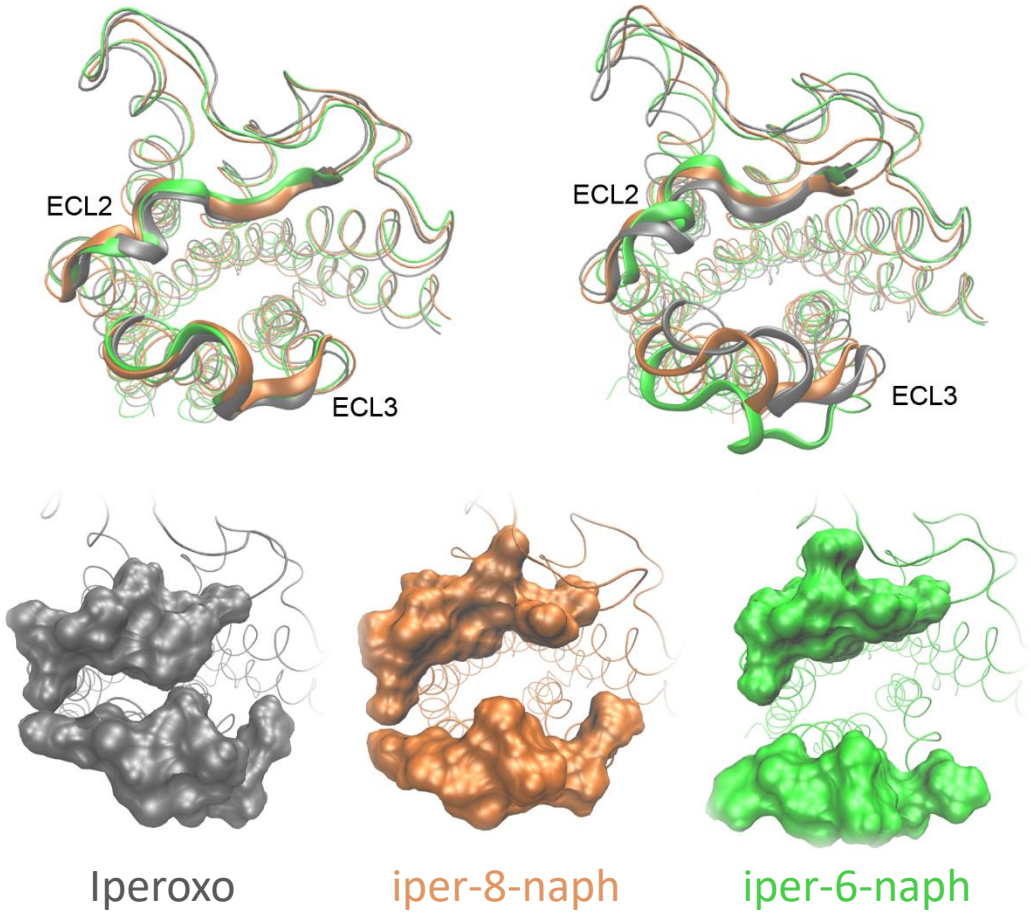


Hampered rearrangement of the allosteric vestibule results in a G_i bias

Conformational intererence with allosteric coupling results in biased signaling

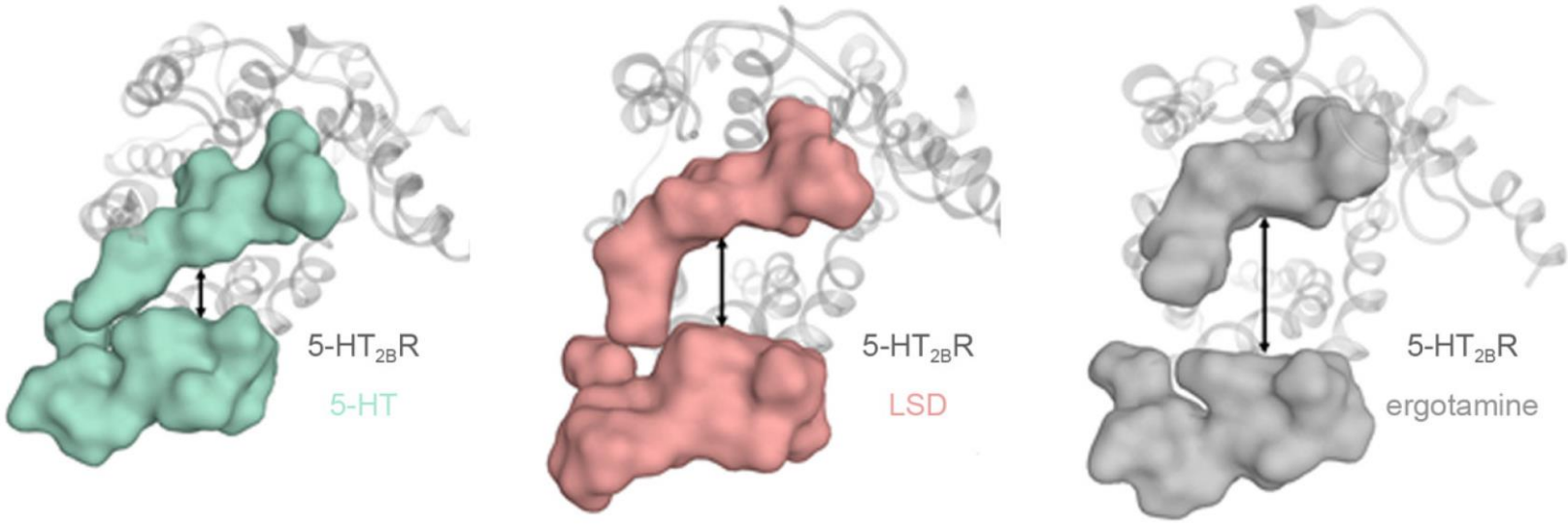
Bermudez and Bock et al., *ACS Chem Biol*, **2017**

G protein selectivity vs. biased signaling



Bermudez and Bock et al., *ACS Chem Biol*, **2017**

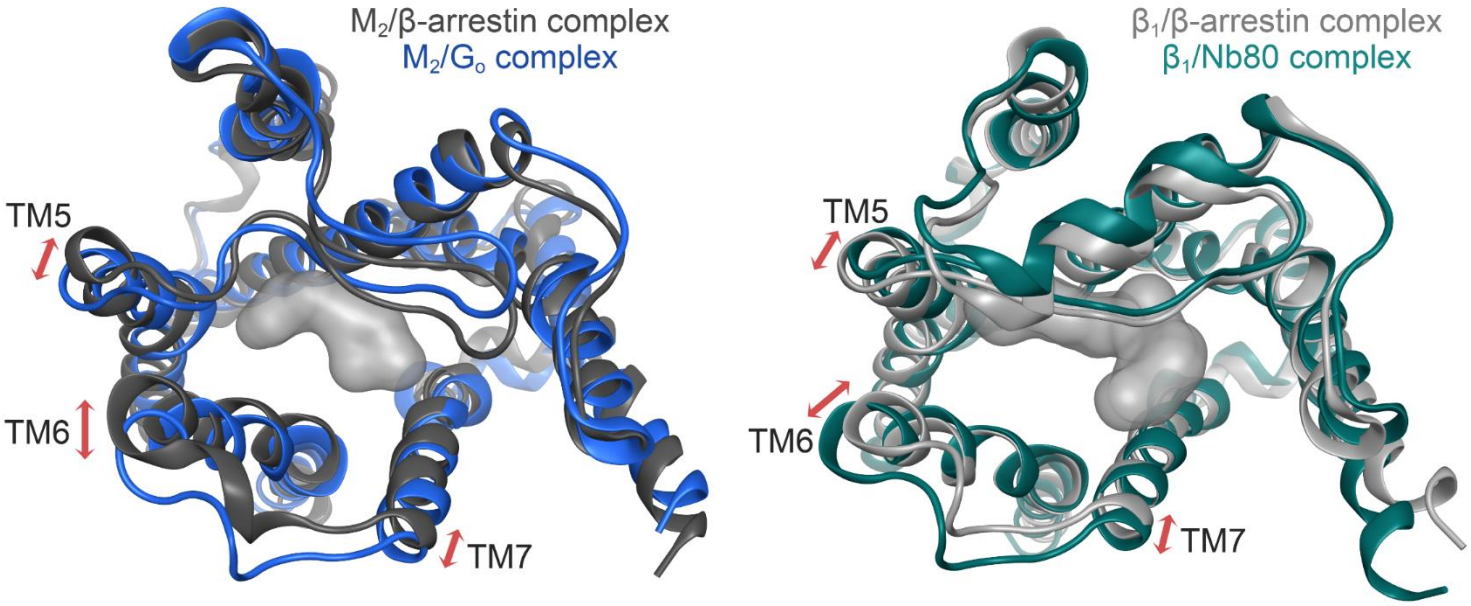
Does this mechanism apply to other aminergic GPCRs?



Our data on 5-HT_{2B} receptors suggest a transferable mechanism

Denzinger et al., IJMS., **2020**

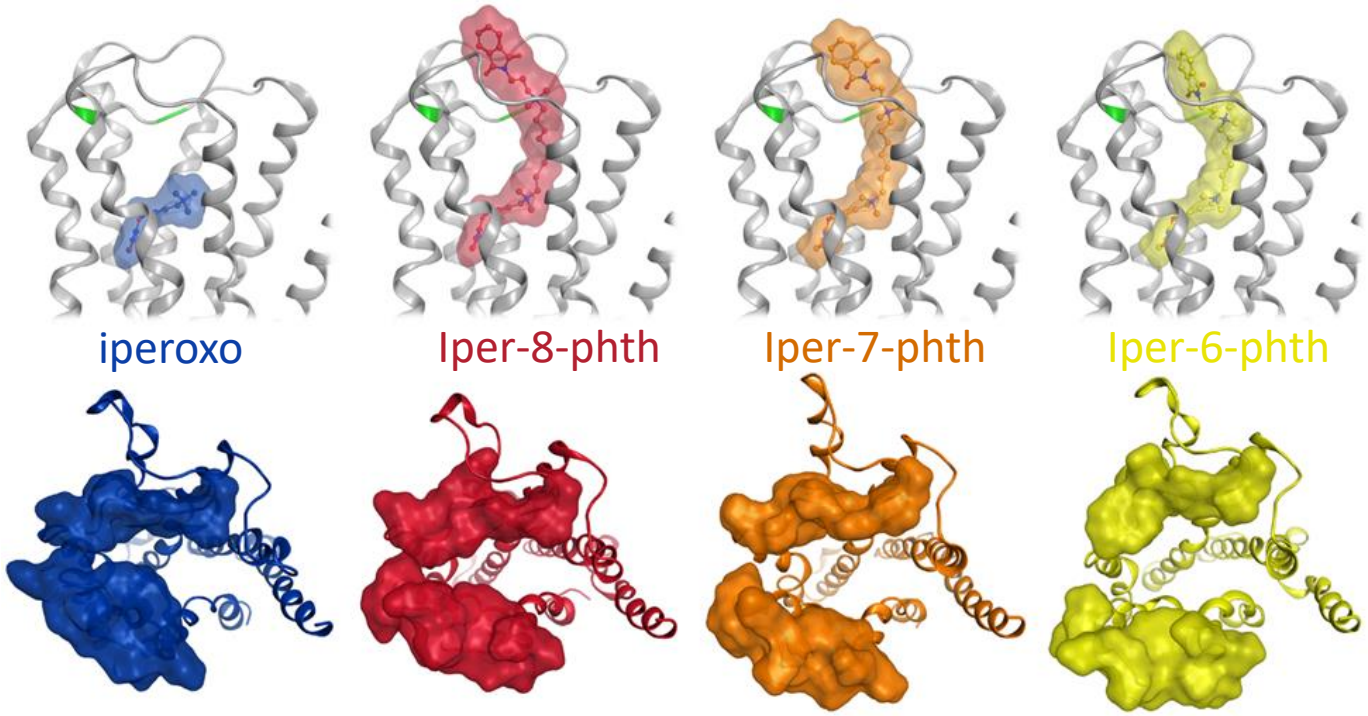
What differences occur when comparing *G protein-bound* and arrestin-bound receptor conformations?



Major differences occur at similar regions when compared to general receptor activation

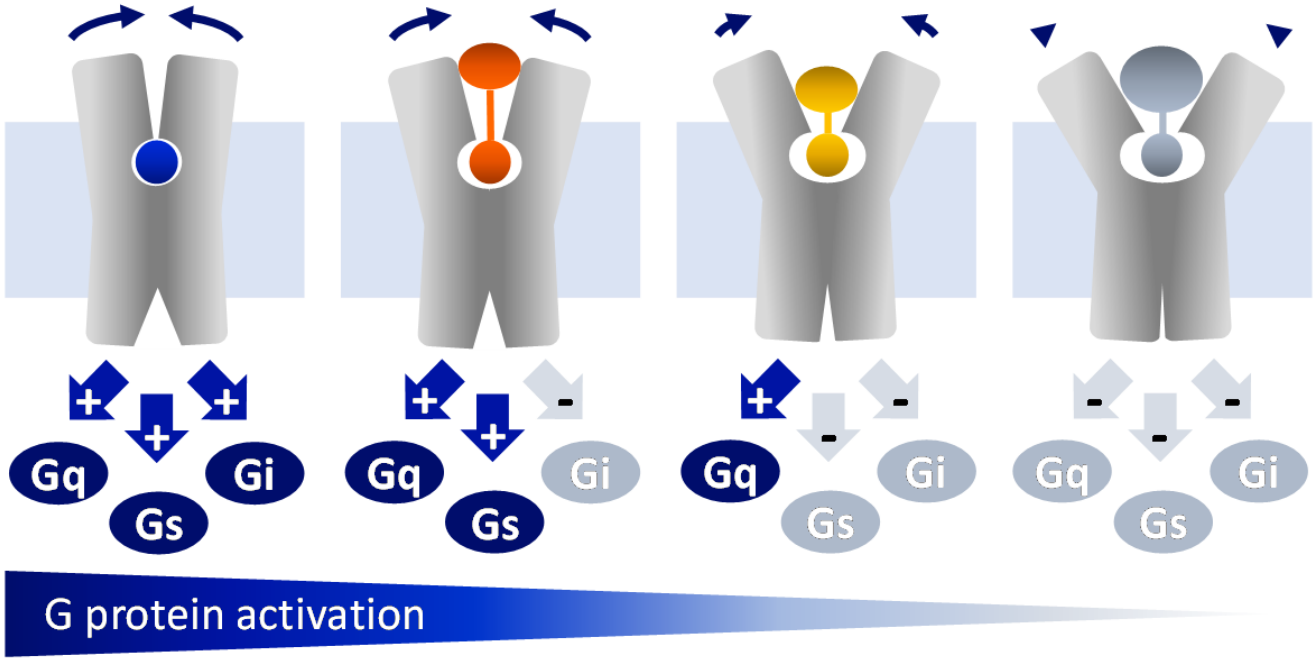
Bermudez and Bock, *Trends Pharmacol. Sci.*, **2019**; Bock and Bermudez, FEBS J., **2021**

Can we fine-tune G protein preferences with biased ligands?



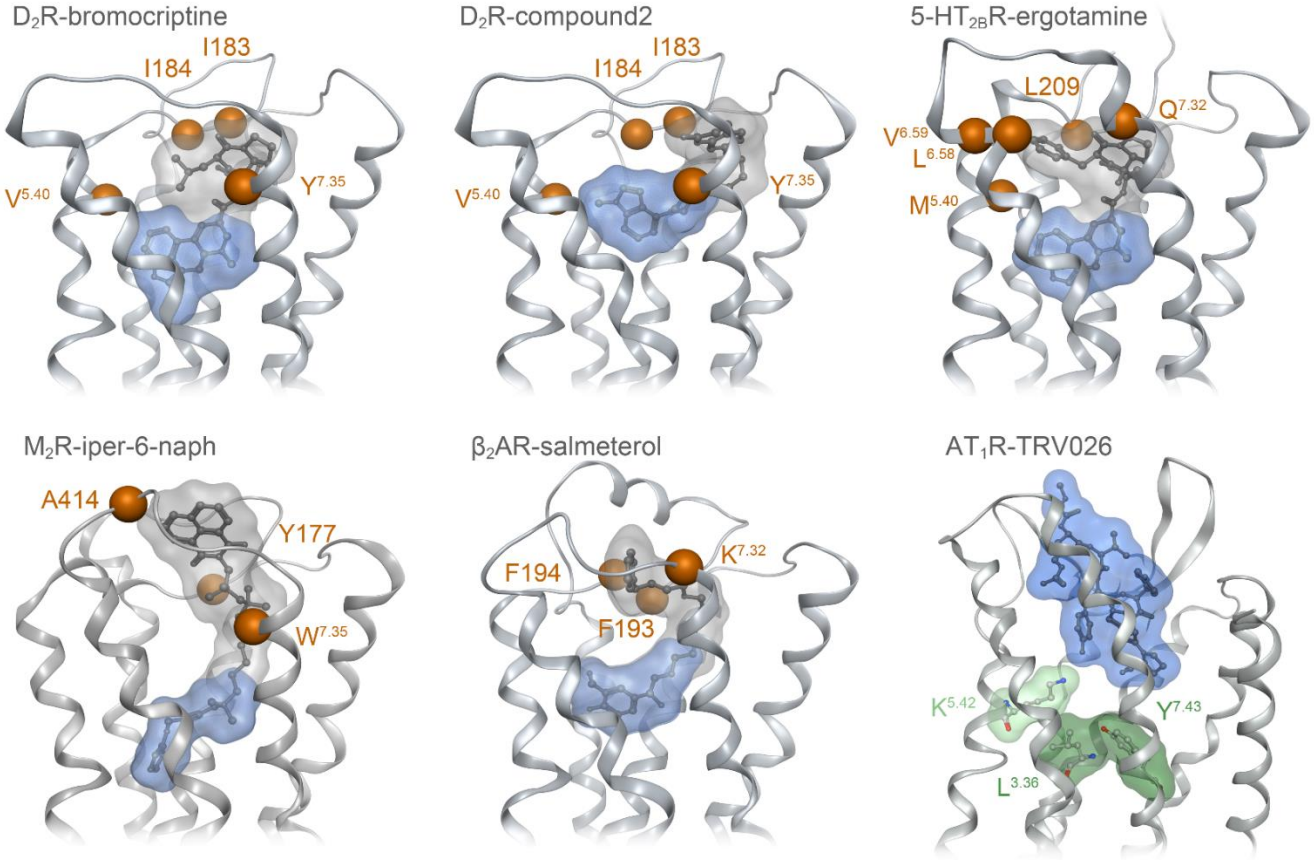
Holze and Bermudez, ACS Pharmacol. Transl. Sci., **2020**

Fine-tuning G protein preference with biased ligands



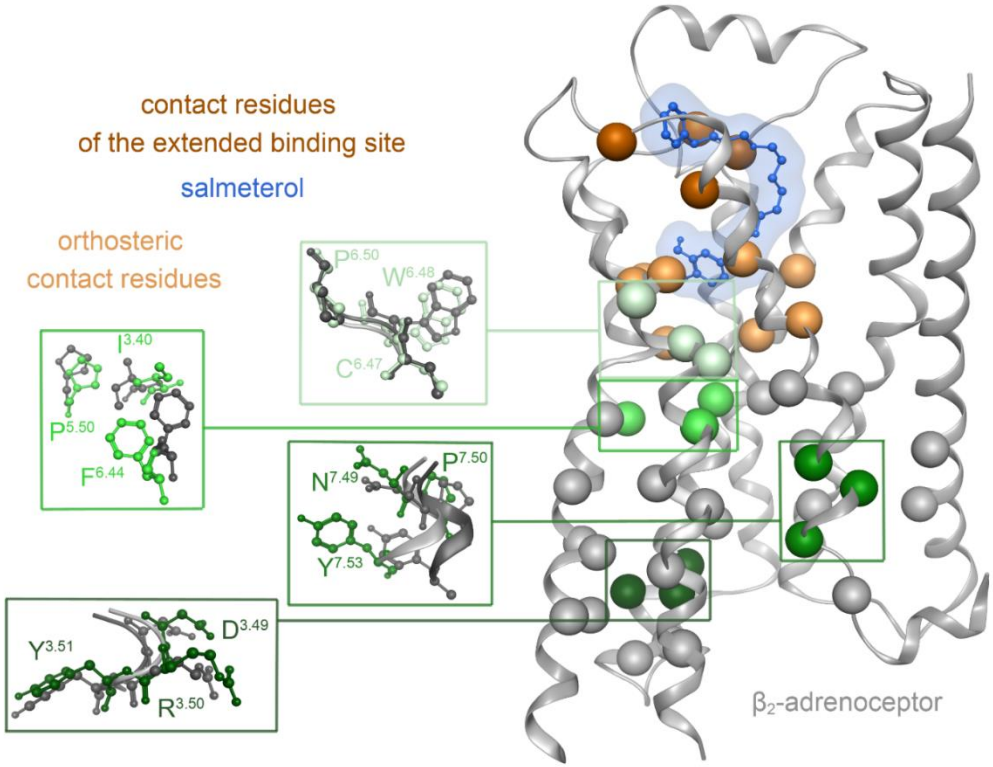
Holze and Bermudez, ACS Pharmacol. Transl. Sci., **2020**

Biased signaling by divergent binding pocket closure



Bermudez and Bock, *Trends Pharmacol. Sci.*, **2019**; Bock and Bermudez, FEBS J., **2021**

Conclusion



Extending a ligand's molecular structure towards the extracellular loop region is a likely source for biased ligands.

While this concept provides a way to design biased ligands, it remains challenging to design biased ligands with a desired signaling profile.

Hotspot residues and hierarchical preferences are receptor (subtype)-specific and might not be transferable

Acknowledgments

MOLECULAR DESIGN.LAB

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DFG Deutsche Forschungsgemeinschaft

DAAD

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Minerva Stiftung

…and all tax payers