In-silico modeling of human, rat, and humanized rat bradykinin B2 receptor-deucrictibant complexes

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Conflict of Interest Disclosure

This work was conducted as a scientific collaboration with Pharvaris Netherlands B.V.

I declare no personal financial competing interests.

This presentation includes data on an investigational product that has not yet been approved by regulatory authorities.

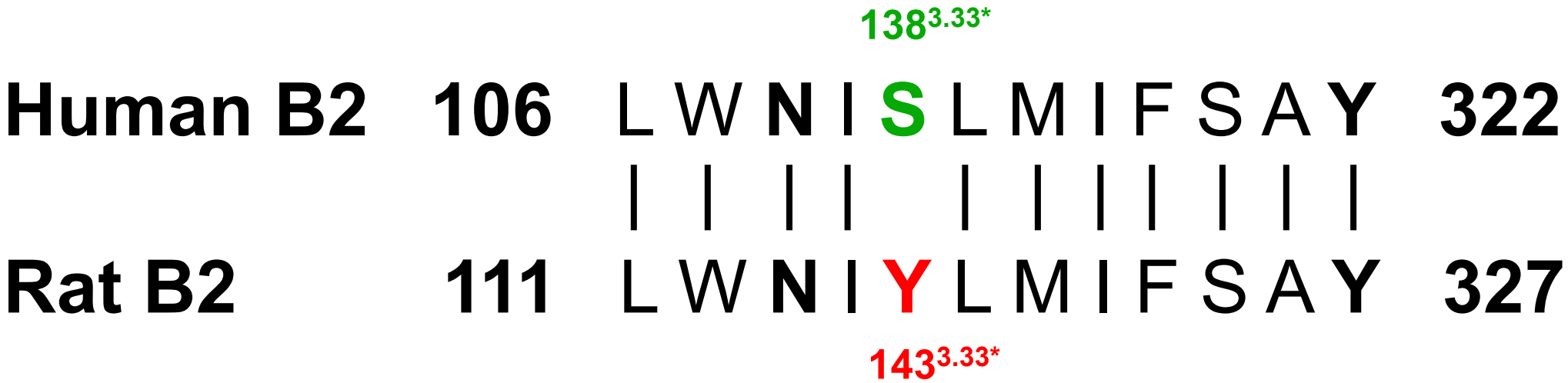
Potency of the small molecule bradykinin B2 receptor antagonist deucrictibant is species-dependent

Species	Antagonist potency K_b* (nM)
Human	0.15
Monkey	1.4
Rat	~180
Rabbit	~300
Mouse	~480
Dog	~2700

*Equilibrium dissociation constant derived from a functional, recombinant calcium mobilization assay (Lesage et al. 2022)

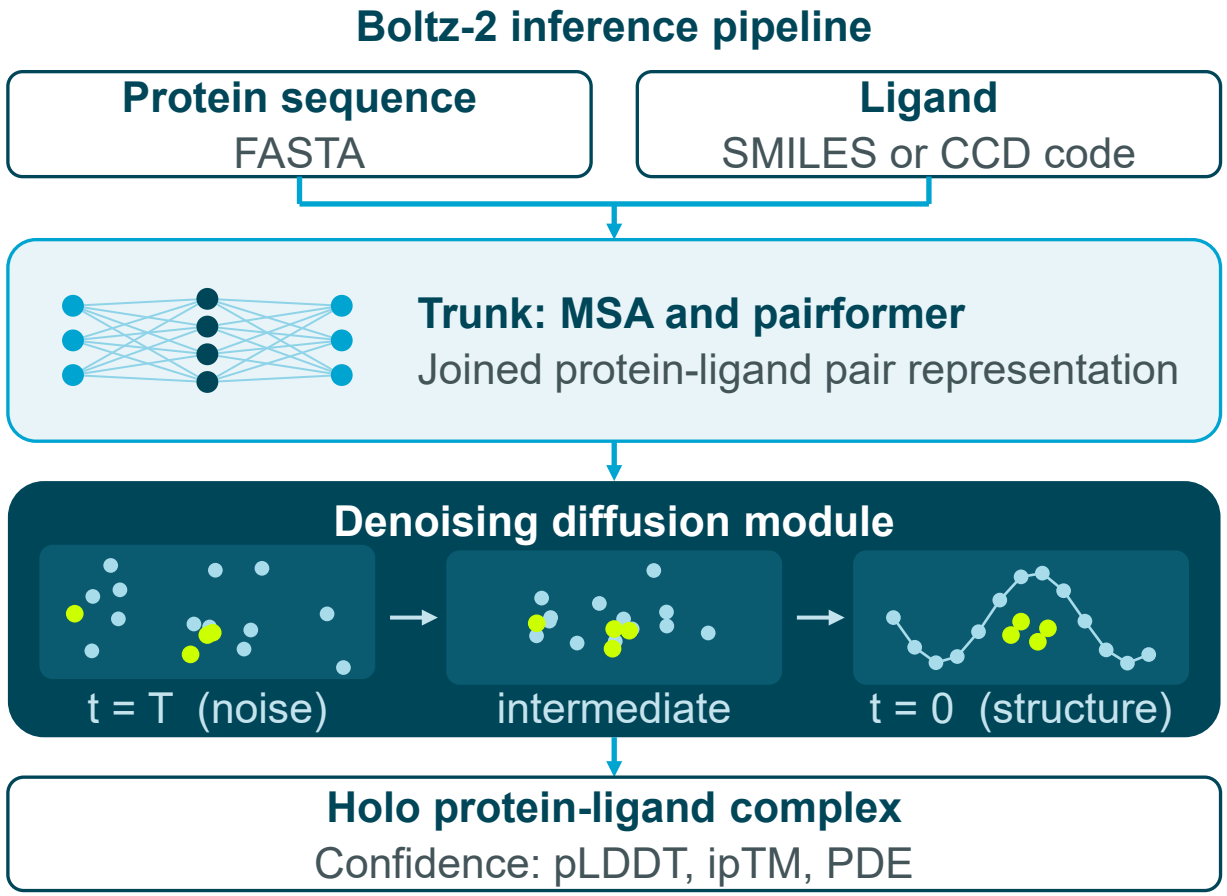
Structural basis of species differences in the bradykinin B2 receptor

Binding-site residue alignment



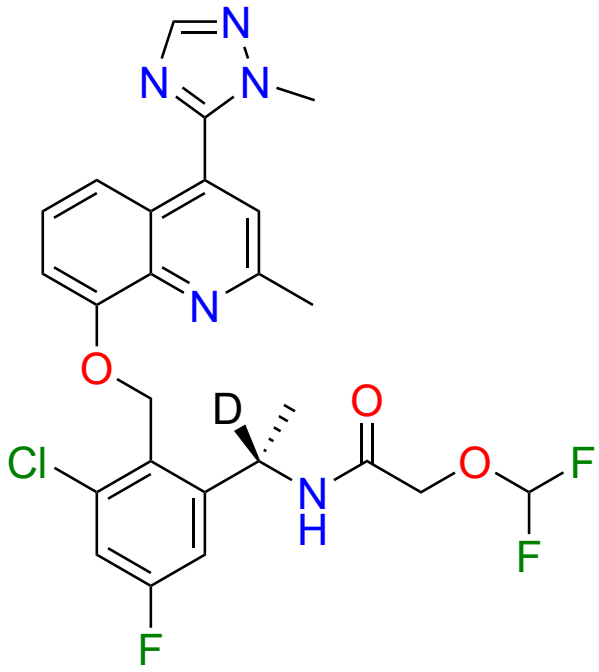
* Position according to the Ballesteros-Weinstein-System. Same numbering denominates homologous regions in Class A GPCRs.

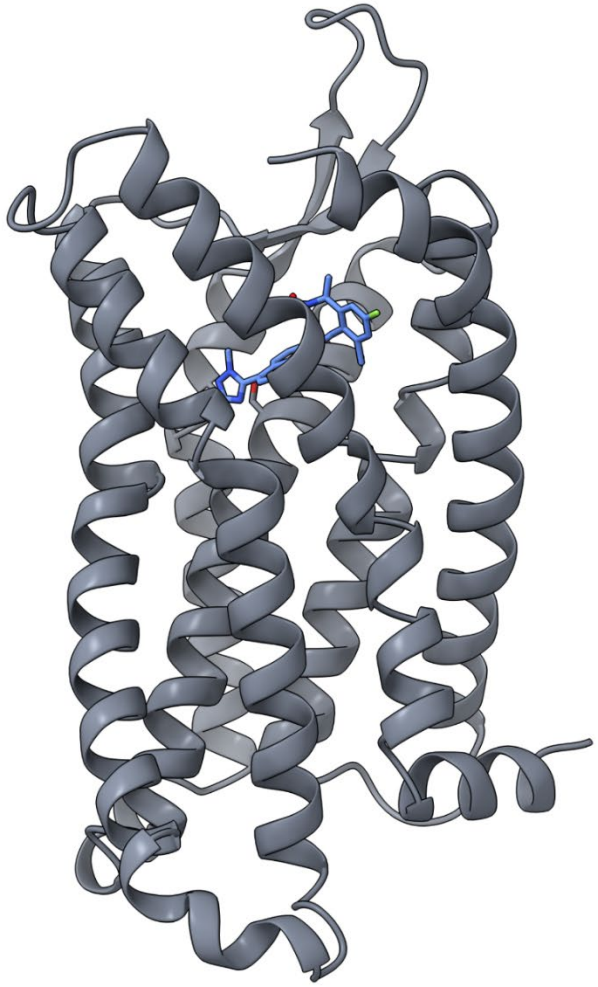
In silico modeling of bradykinin B2 receptor-deucrictibant interaction

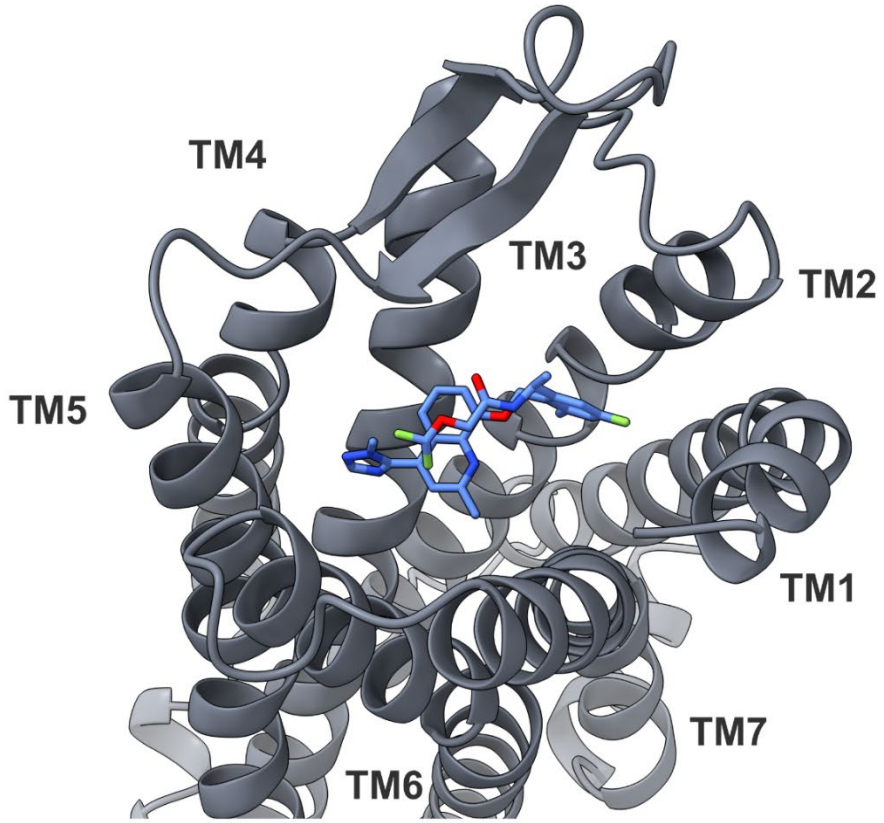


FASTA, sequence format; SMILES, Simplified Molecular Input Line Entry System; CCD, Chemical Component Dictionary; MSA, Multiple Sequence Alignment; pLDDT, predicted Local Distance Difference Test; ipTM, interface predicted Template Modeling score; PDE, Predicted Distance Error.

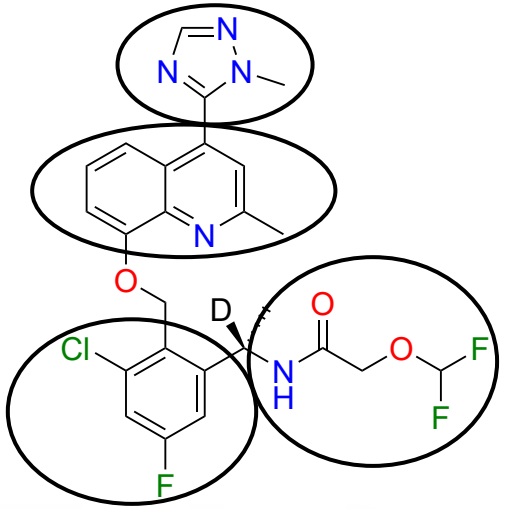
Deucrictibant is positioned in the orthosteric binding site of the human bradykinin B2 receptor



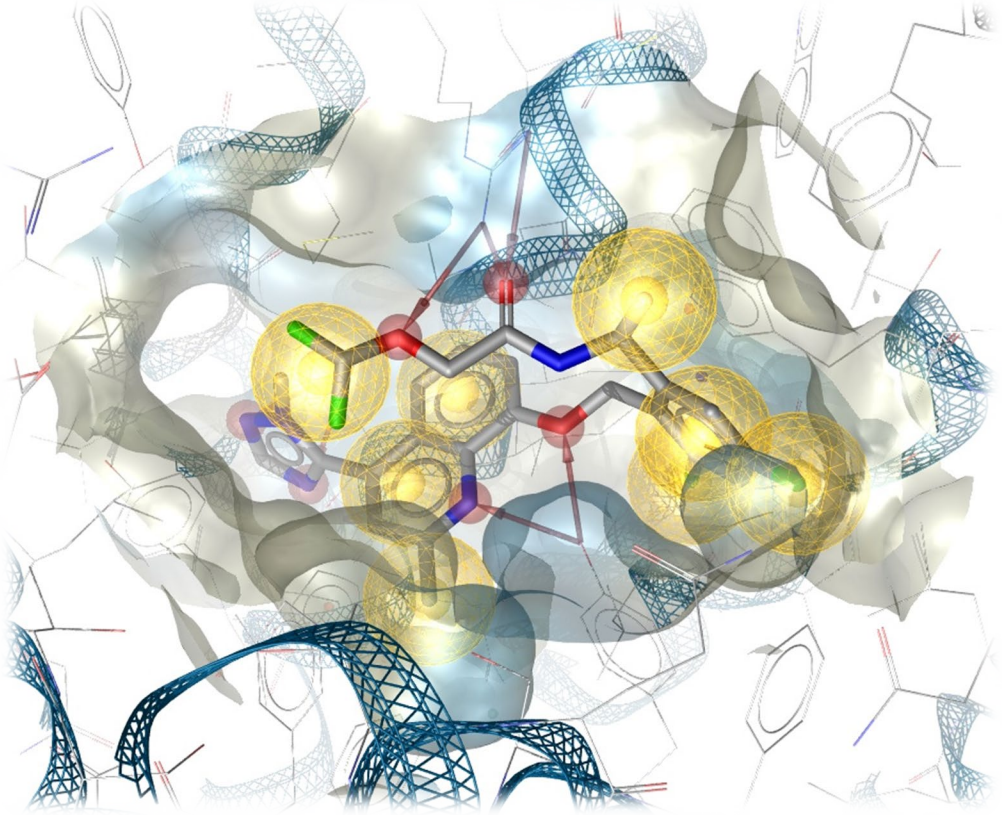




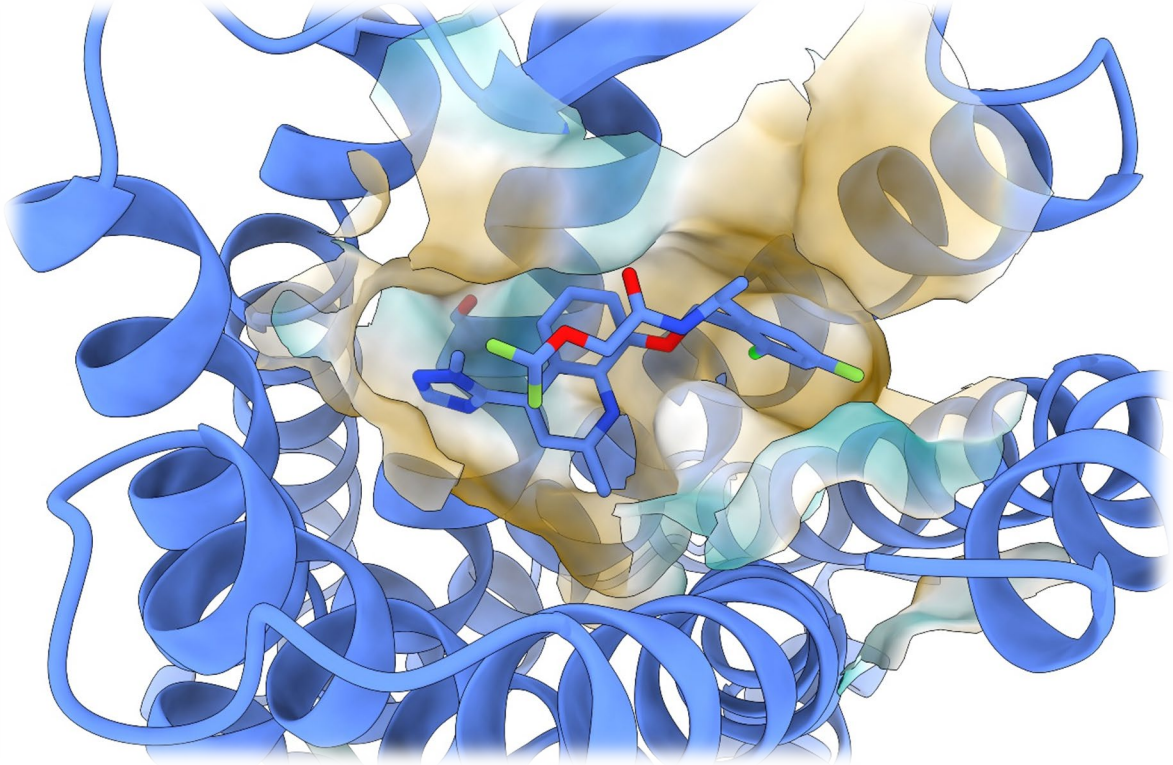
Protein-ligand interaction analysis



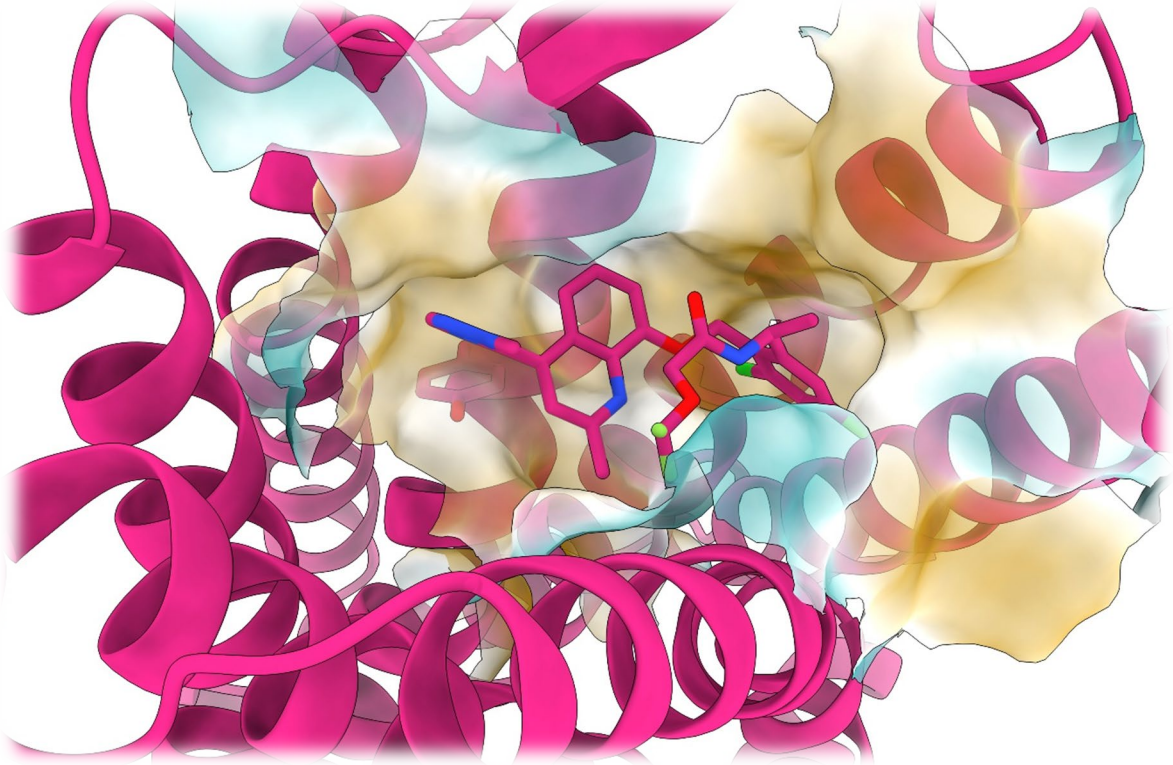
- 2-Methylquinoline core positioned at the base of the binding pocket
- Halogenated phenyl interacting with hydrophobic regions on TM1/TM2/TM7
- Peptide-like tail wrapped above deucrictibant toward the extracellular region
- Triazole positioned in a sub pocket towards TM3/TM4 → hydrogen bonding with **S138$^{3.33}$**



Triazole sub-pocket occluded in the rat receptor

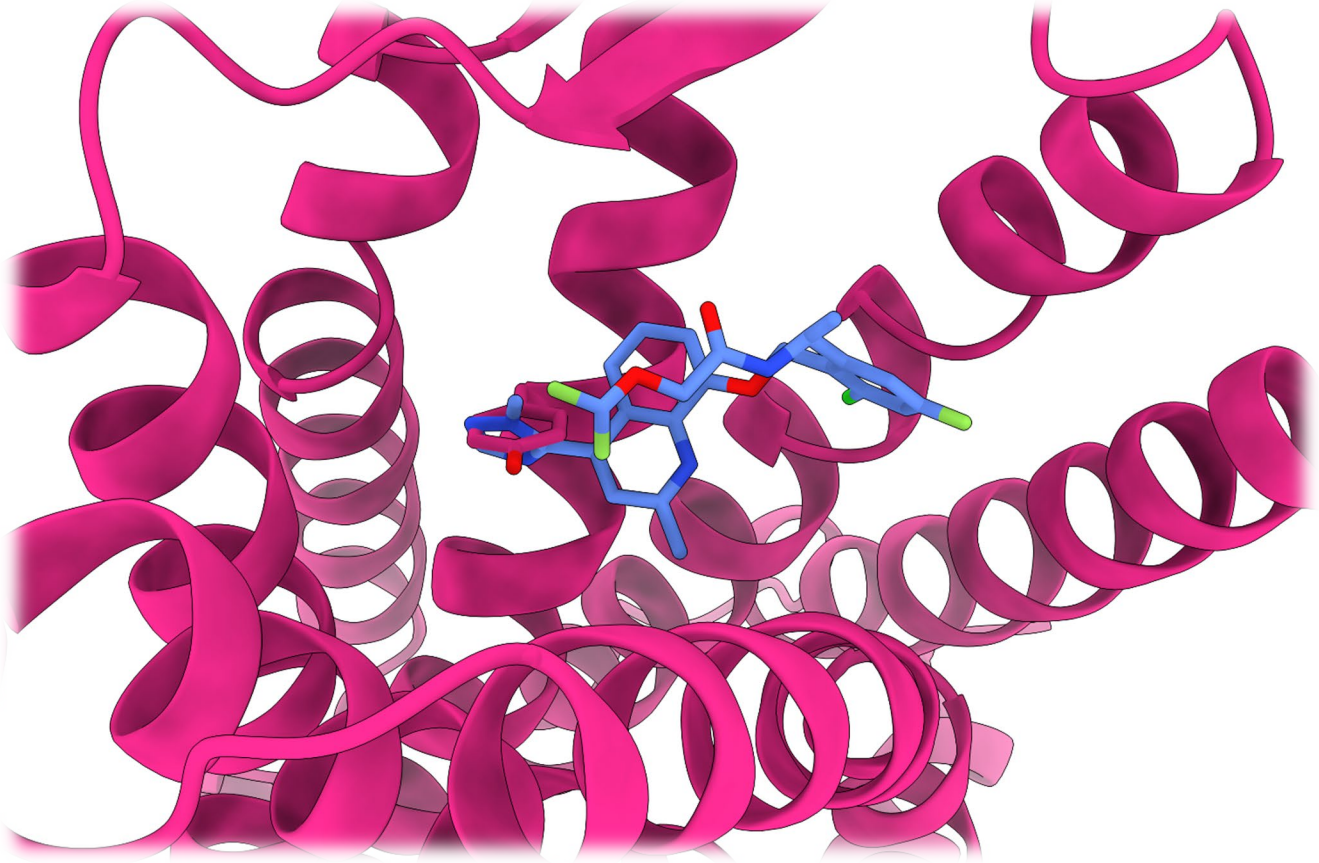


Human



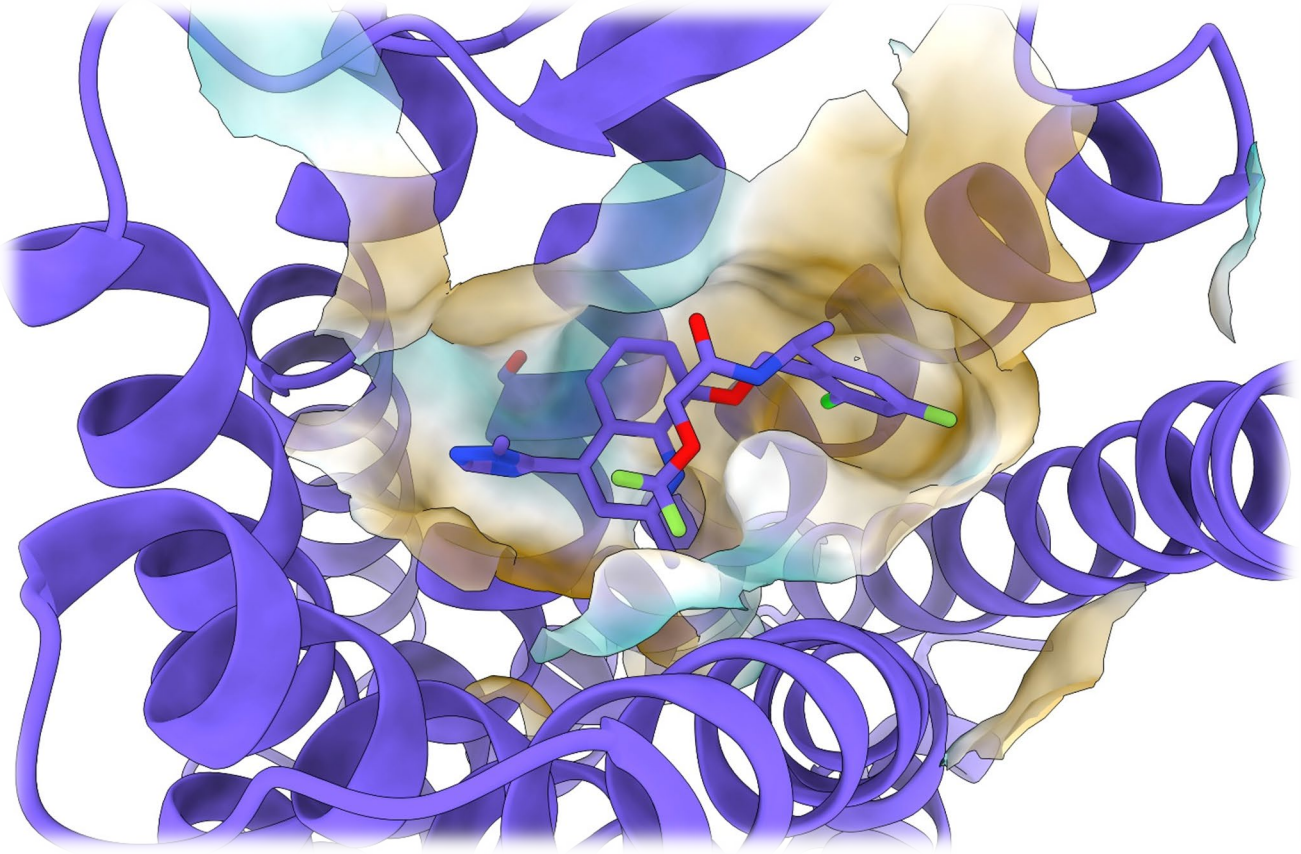
Rat

Triazole sub-pocket blocked in the rat receptor



Human binding pose
in rat receptor

Humanization of rat receptor by Y143S substitution restores human-like fit and activity of deucrictibant



Y143S transgenic rat bradykinin B2 receptor

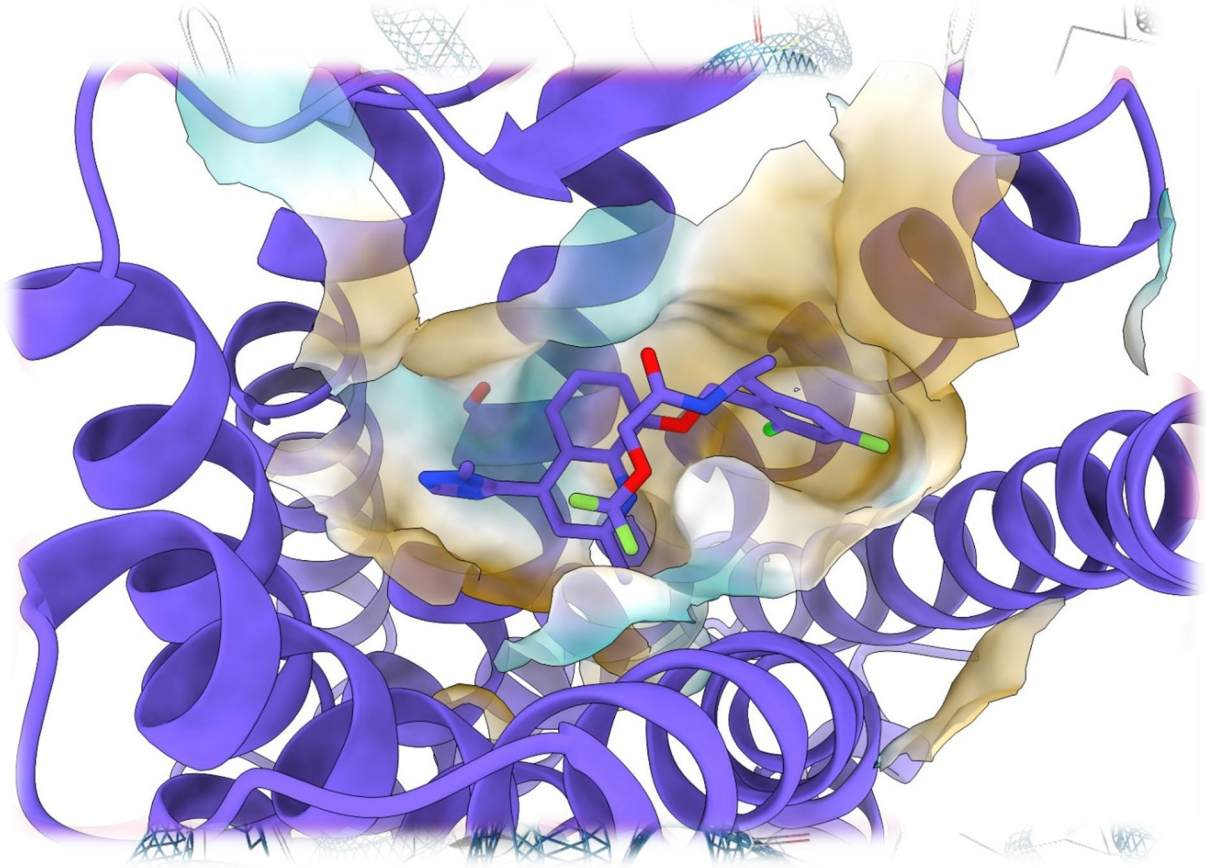
Species	Antagonist potency K_b* (nM)
Human	0.15
Rat	~ 180
TG Rat	0.45

* Kb based on functional calcium mobilization assay; data partially unpublished.

Kb, equilibrium dissociation constant; TG, transgenic.

Conclusion

- Established the binding mode of deucrictibant in the human bradykinin B2 receptor
- Identified a TM3/TM4 sub-pocket as the determinant of species-dependent potency
- Position 3.33 gates the TM3/TM4 sub-pocket with serine in responsive and tyrosine in non-responsive species
- Humanized Y143S transgenic rat serves as a tool for investigating small molecule bradykinin B2 receptor antagonists in vivo



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