

In silico Modeling of Human, Rat, and Humanized Rat Bradykinin B2 Receptor-Deucrictibant Complexes

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Key takeaways

Our findings demonstrated that a minimal, rationally selected genetic modification is sufficient to overcome a species-related barrier in the bradykinin B2 receptor binding and antagonist potency of deucrictibant. The humanized *Y143S* bradykinin B2 receptor transgenic rat represents a validated model for studying the pharmacological effects of small molecule bradykinin B2 receptor antagonists.



Deucrictibant binding mode in the human bradykinin B2 receptor was established



TM3/TM4 subpocket was identified as the determinant of species-dependent potency



A single amino acid at position 3.33, serine in responsive, and tyrosine in non-responsive species, gates the TM3/TM4 subpocket



Humanized *Y143S* transgenic rat serves as a tool for investigating small molecule bradykinin B2 receptor antagonists in vivo

This presentation includes data for an investigational product not yet approved by regulatory authorities.

Background

- Deucrictibant** is an orally bioavailable, selective bradykinin B2 receptor antagonist under development for both prophylactic and on-demand treatment of bradykinin-mediated angioedema attacks.¹⁻⁸
- Structural species differences** in the bradykinin B2 receptor complicated preclinical evaluation of the small-molecule antagonist deucrictibant intended for human therapy.

Objective

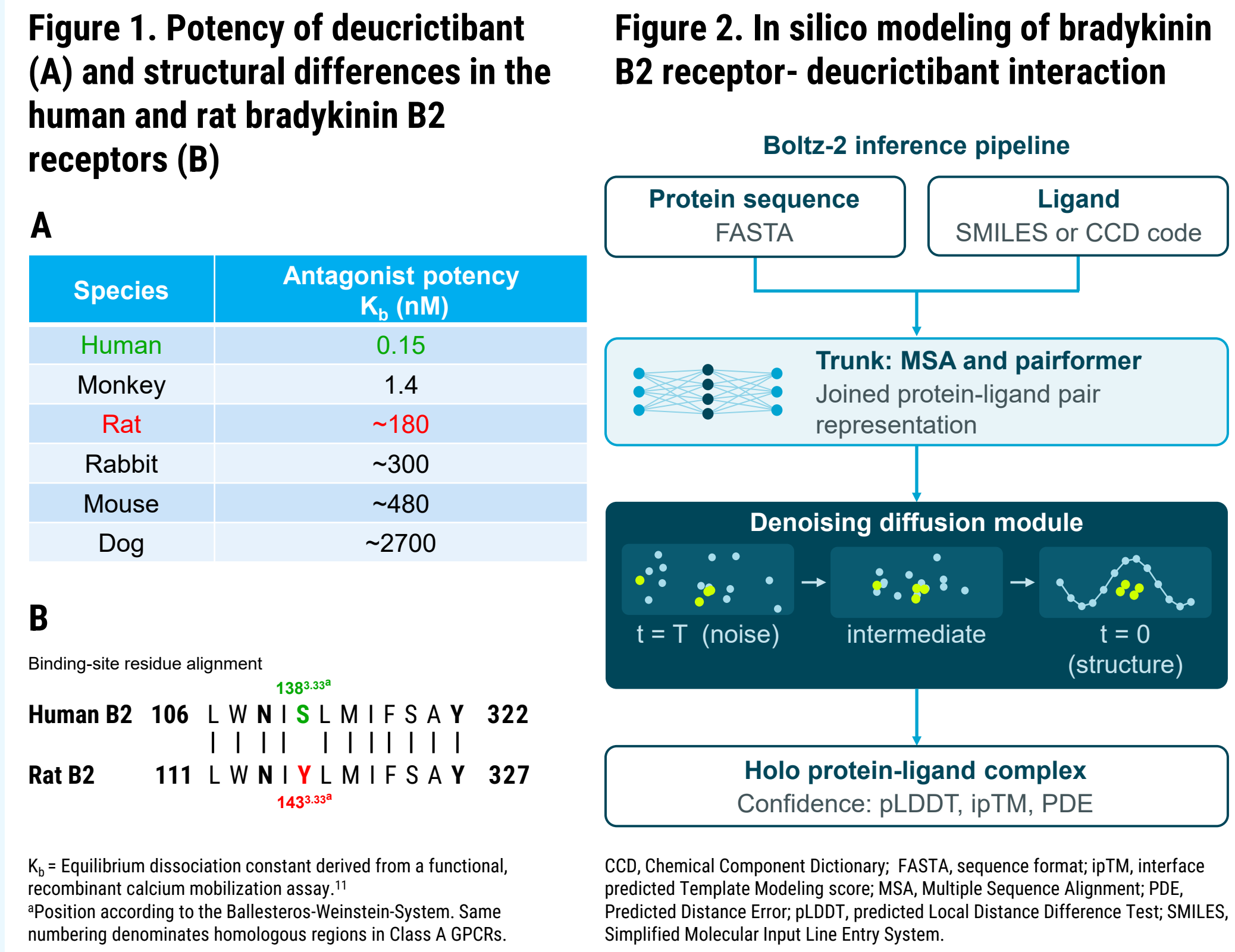
To investigate whether an amino acid at a key position within the rat bradykinin B2 receptor binding pocket is responsible for the reduced affinity and antagonist potency of the human-targeted clinical candidate deucrictibant.

Methods

- Human, rat, and humanized rat receptor-ligand complexes were modeled through the open-source software Boltz-2 designed for predicting biomolecular interaction and co-folding.⁹
- Subsequently, 3-D pharmacophore analysis was conducted using LigandScout¹⁰ and the Dynophores.
- A transgenic humanized knockin rat leading to the *Y143S* amino acid substitution in the bradykinin B2 receptor protein was generated using CRISPR-Cas9 technology.
- Antagonist potency was assessed using calcium mobilization assays in the mammalian cell line HEK293 recombinantly expressing the bradykinin B2 receptor.

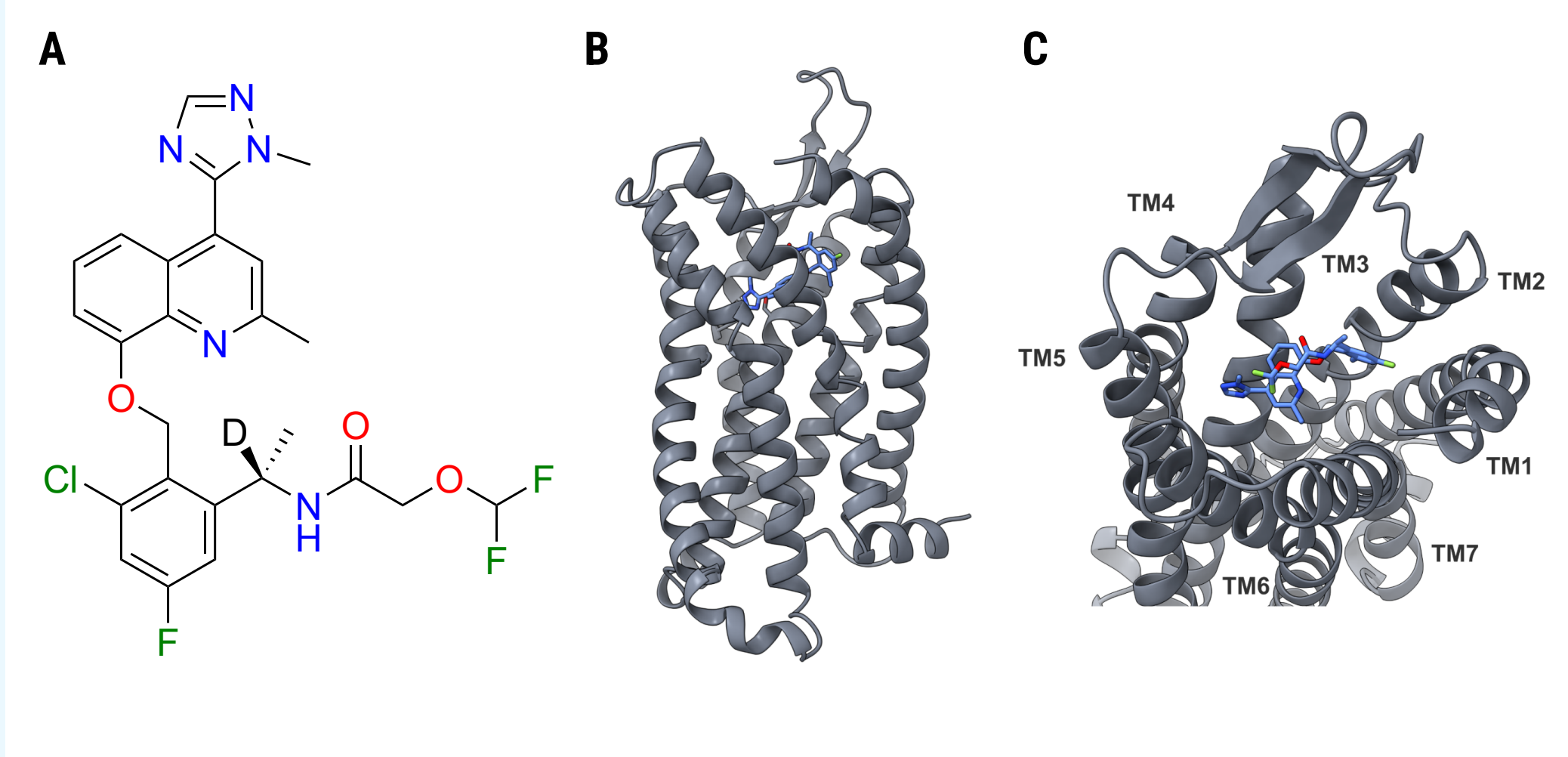
Results

- Potency of the small molecule bradykinin B2 receptor antagonist deucrictibant is species-dependent (**Figure 1A**).
 - We previously established a transgenic humanized rat by introducing a single amino acid change from tyrosine (Y) to serine (S) at position 143 of the canonical sequence of the rat bradykinin B2 receptor (**Figure 1B**).
- In Silico interaction and co-folding methods revealed how deucrictibant binds to the bradykinin B2 receptor and the effects of the *Y143S* mutation (**Figure 2**).

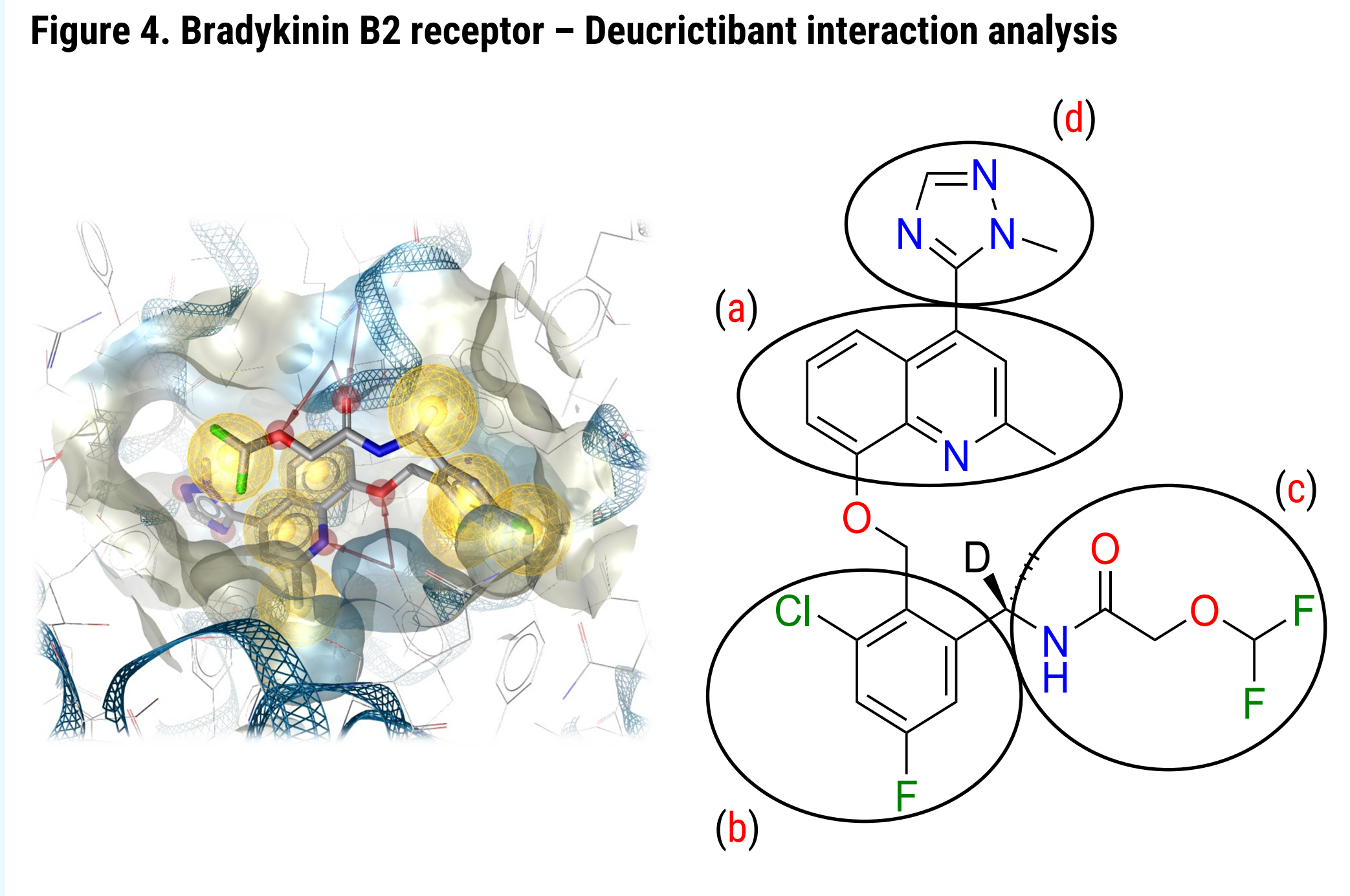


- In the human receptor, deucrictibant forms stable hydrogen bonds to S138, anchoring it in the orthosteric binding pocket (**Figure 3**).

Figure 3. Molecular model of deucrictibant (A) positioned in the human bradykinin B2 receptor (B and C; different magnifications)



- Protein-ligand interaction analysis showed (**Figure 4**) that:
 - The 2-methylquinoline core of deucrictibant is positioned at the base of the binding pocket (**a**).
 - Halogenated phenyl interacted with hydrophobic regions on TM1/TM2/TM7 (**b**).
 - The difluoromethoxyacetamido group is positioned toward extracellular loop 2 (EC2) and interacts with Arg196 at position 4.64 of TM4 (**c**).
 - Triazole positioned in a subpocket towards TM3/TM4 → hydrogen bonding with S138^{3.33} (**d**).



- In the wild-type rat receptor, the bulkier Y143 blocks the triazole subpocket and thus shifts deucrictibant away from its optimal human receptor binding mode into a weaker orientation (**Figures 5 and 6**).

Figure 5. Deucrictibant in its species-specific predicted binding pose at the human and native rat bradykinin B2 receptor

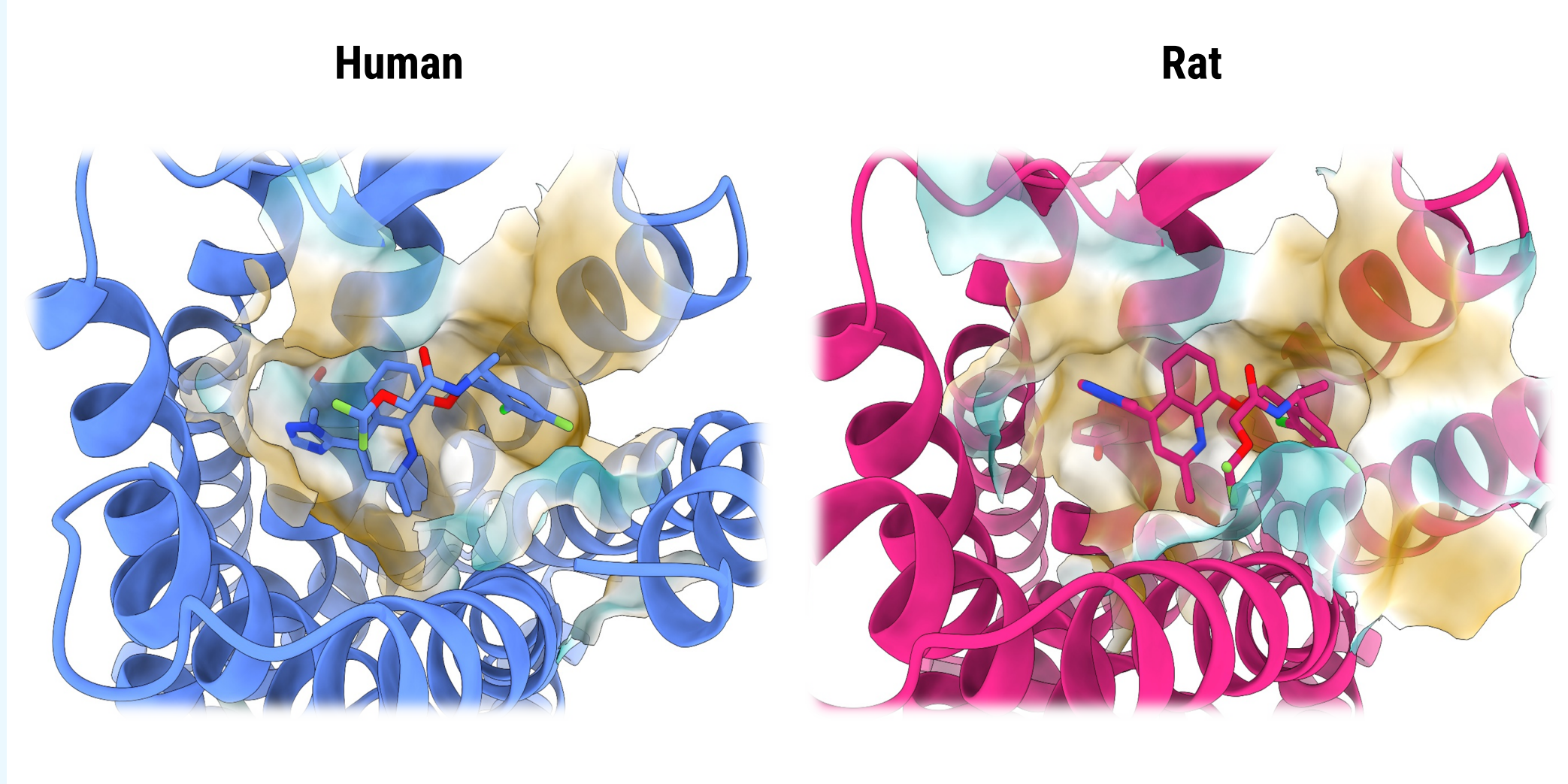
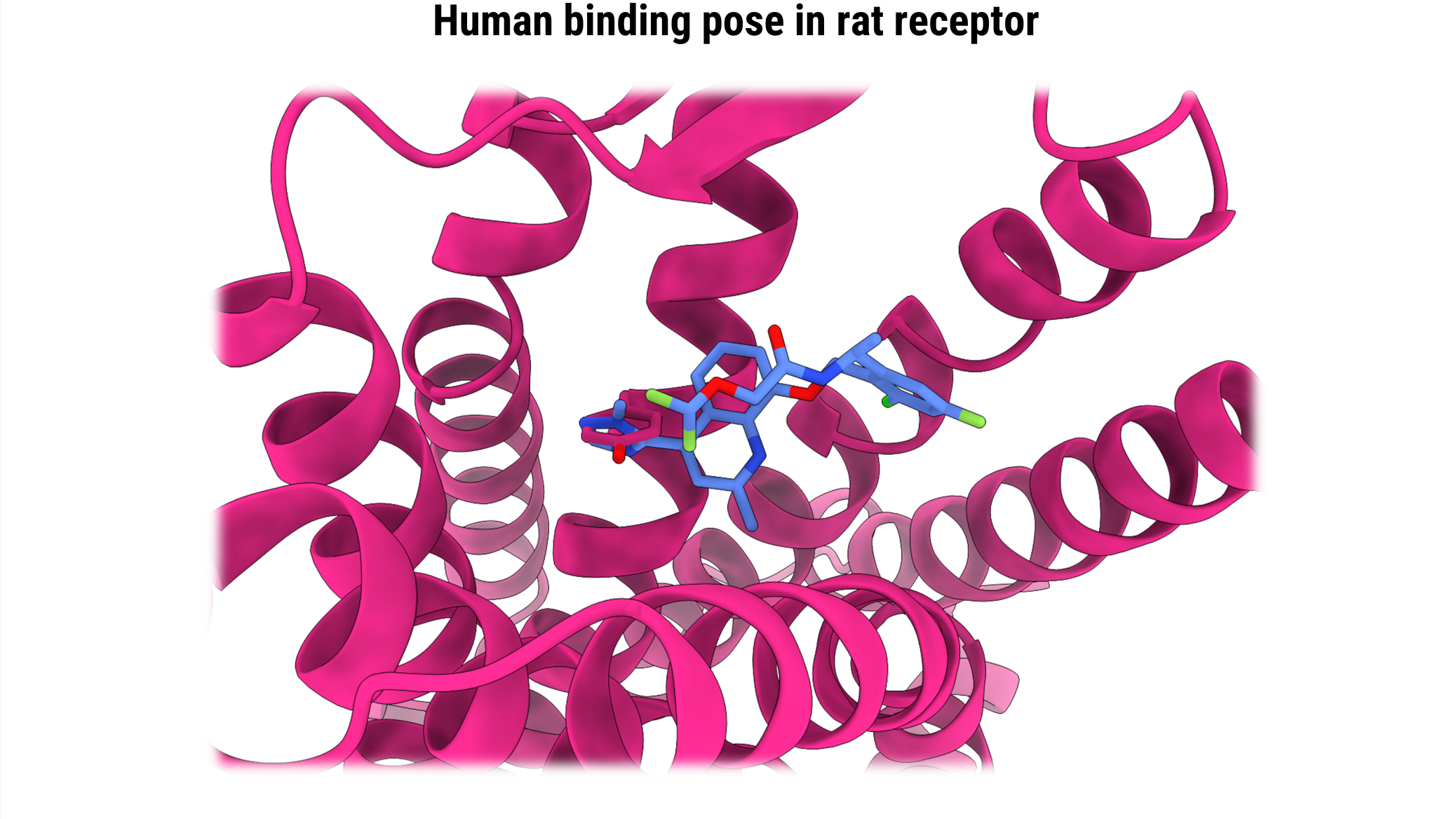
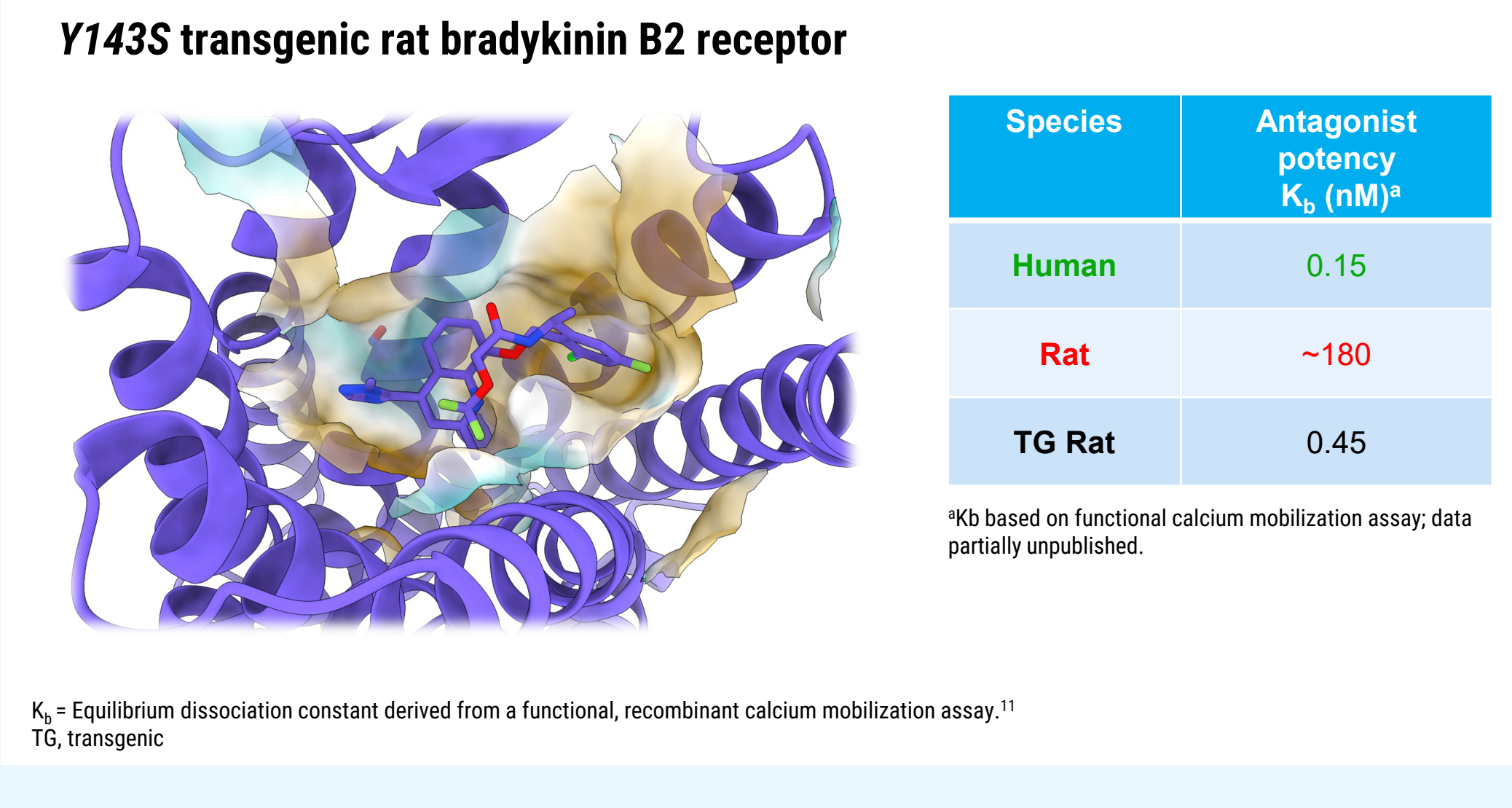


Figure 6. Human binding pose in the native rat receptor illustrating the sterical hindrance



- These in silico analyses confirm the amino acid at position 143 of the rat bradykinin B2 receptor as the structural determinant governing the loss and rescue of deucrictibant activity (**Figure 7**).

Figure 7. Humanization of rat receptor by *Y143S* substitution restores human-like fit and activity of deucrictibant



References

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