3D Modeling of ZCZ011 at CB_1 Receptors & Applications in Experimental Neuroscience

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References and Contributions:

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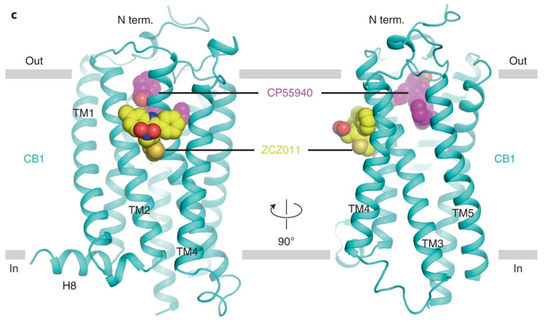
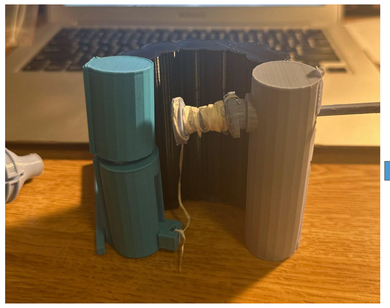
Introduction

- CB_1Rs are Gi-protein coupled receptors.
- 7 transmembrane alpha-helices and 1 C-terminus, intracellular helix[1]
- ZCZ011 is an allosteric agonist in CB_1R cAMP pathways but a PAM in pERK activation and β-arrestin recruitment[2,3]
- Binding site of ZCZ011 is distinct from the orthosteric binding site[4]
- ZCZ011 binds an extra-helical binding domain on the upper half of TMH 2-3-4[1].
- Distance of 7.9 Å from the orthosteric site[1].
- TMH6 and TMH2 rearrangement critical for CB_1R activation[1,5]
- ZCZ011 stabilizes the active state and promotes the rearrangement of TMH2[1,5]

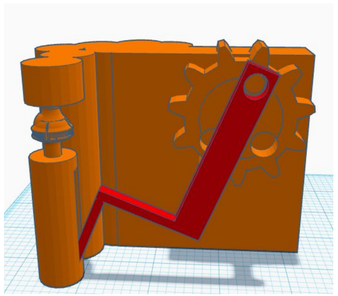


Iterative Design Process

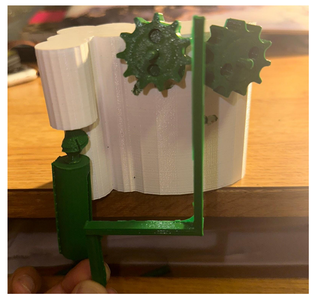
Low Fidelity Prototype



First Print Model

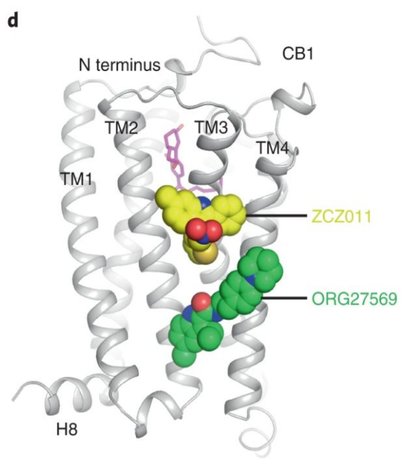


Final TinkerCad Model



Midterm Print Model

Final Print Model



Troubleshooting and Future Directions:

- First print model design was complicated, resulting in a unstable 3D model
- First print model wasn't functional.
- Midterm Model was more stable, but unfunctional due to the failed movement of the connector
- Future models should include a more complicated design that includes both allosteric modulation and agonism of ZCZ011

Methods and Materials

- Design-Related Research.
- Low-Fidelity Prototyping.
- Sketching.
- 3D Model Design in TinkerCAD
- Makerspace.
- Iterations and Prototyping.

BEAM

Conclusions

- Applications of CB1 allosteric agonist ZCZ011 include treatment of opioid use disorder (OUD).[6]
- Modern medications utilized are limited by their abuse potential and minimal efficacy.[6]
- Allosteric agonist ZCZ011 amplifies CB1 receptor signaling and reduces pain in animal models.[6]
- Extensive weight loss secondary to naloxone use can be treated by ZCZ011.[6]
- ZCZ011 could serve as an innovative OUD medication.[6]

Video Demonstration

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