Predicting the Conformational Change of the 5-HT-2C Receptor in Response to CTW0415: Applications in Treating Substance Use Disorder

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Citations and Contributions

Background

Substance use disorder is an increasingly relevant issue that has yet to be fully explored in terms of pharmacological treatment. The **serotonin subtype 2C (5-HT-2C) receptor** has found to be a potential target for treatment.

- The 5-HT-2C receptor has a major influence on **dopamine inhibition.**[5,6]
- The 5-HT-2C receptor is also implicated in **influencing the effects of antipsychotics.**[4]

CTW0415 is a **positive allosteric modulator (PAM)** to the 5-HT-2C receptor that has implications in treatment.

- CTW0415 acts at a **spatially distinct** 5-HT-2C receptor allosteric binding site.

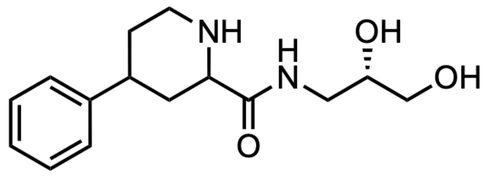


Figure 1: The chemical structure of CTW0415[1]

Part 1: Protein Characterization

Determining the Binding Site

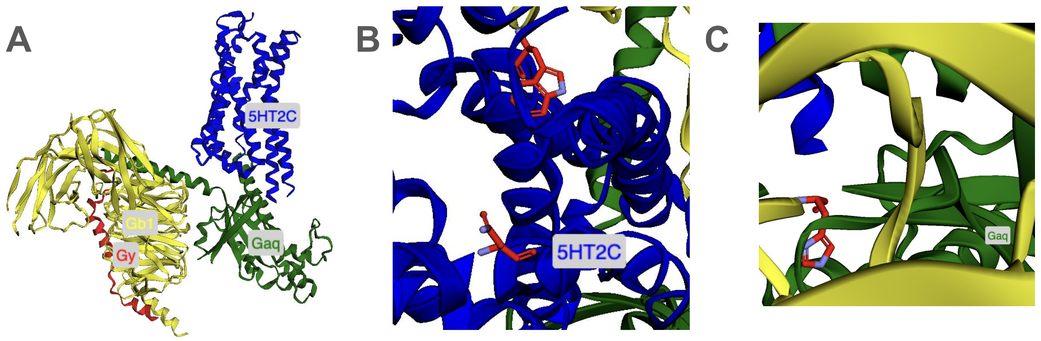


Figure 3: Modeling the the 5-HT-2C receptor A) the 5-HT-2C receptor in the open conformation bound to the Gaq protein complex; B) the CTW0415 binding pocket; C) the 5-HT-2C receptor and Gαq interaction (PDB model, code: 8DPH)

Predicting the the Receptor Change

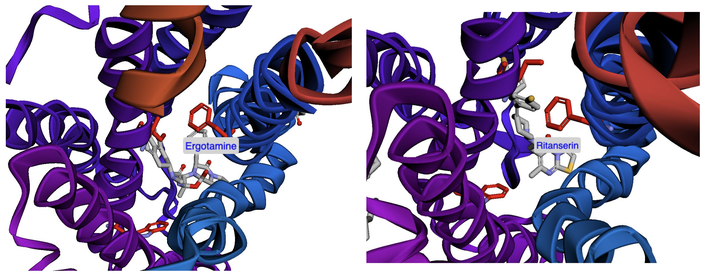
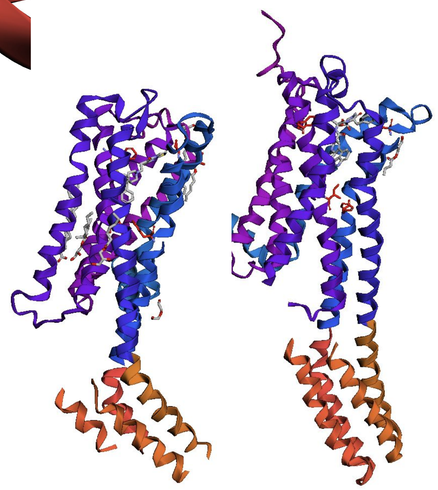


Figure 5: Ritanserin (left) and ergotamine (right) bound 5-HT-2C PDB model, codes: 6BQH, 6BQG

Because CTW0415 interacts with the π-cation interaction of 5-HT-2C bound to Gαq, we suggest that the increased agonist efficacy comes from increased stabilization in Gαq binding.



Materials and Methods

Protein Sequencing and Visualization

WORLDWIDE PDB PROTEIN DATA BANK

Code for building protein model →

Model Building

TINKERCAD

AUTODESK® TINKERCAD®

Part 2: Model Design

The Design Process

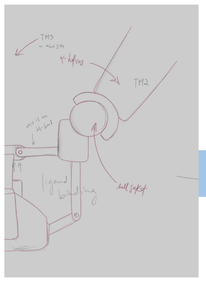


Figure 6: Initial conceptualization

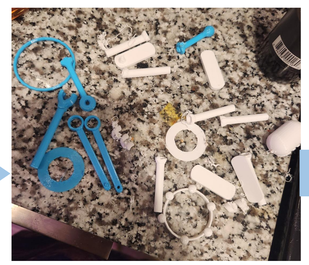


Figure 7: First attempt at 3D printing

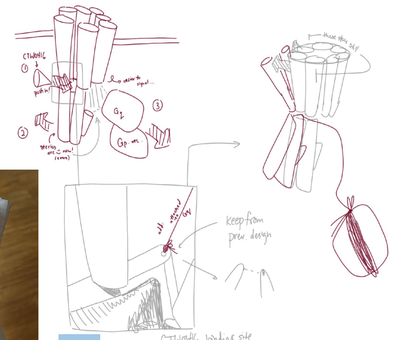


Figure 8: Back to the drawing board

This process is iterative!

Figure 9: Revisiting Ball and Socket Joint model

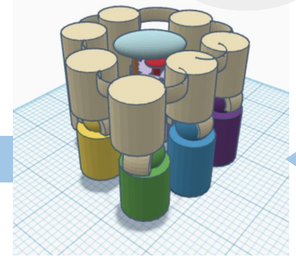


Figure 10: Revising for accuracy

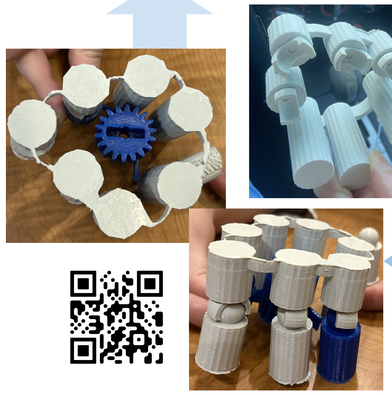


Figure 11: Final Model (placeholder QR code)

Discussion

Implications

Our proposed mechanism illustrates how PAMs target specific interactions within the receptor for treatments to have reduced off-target effects.

- CTW0415 is a compound synthesized for the purpose of creating more 5-HT-2C PAMs in the future,[1] so the mechanism by which CTW0415 acts is crucial for understanding changes to the 5-HT-2C receptor that are involved in its effects.

Future Directions

1. Improve the model to include the twisting mechanism of TM helices 3 and 6.
2. Modify the model to have spatially accurate binding pockets for the agonist and CTW0415.
3. Further model changes to Gαq coupling from CTW0415 binding to the 5-HT-2C receptor.
4. Model the Gαq mechanism.

Acknowledgements

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