



3D Modeling Downstream Effects of Aripiprazole Binding to the D₂ Dopamine Receptor

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Abstract | Background

The drug aripiprazole is an antipsychotic that has gained popularity for its ability to be used to treat schizophrenia without many side effects. It is considered a partial agonist of the D₂ dopamine receptor, a g-protein coupled receptor (1). Aripiprazole alters receptor function by acting on different G proteins. It acts as a partial agonist when binding to the dopamine D₂ receptor, and for Galpha i/o signaling (1). Oppositely, aripiprazole acts as an antagonist for Gβγ signaling. When aripiprazole binds to a D₂ receptor, it results in inhibition of adenylyl cyclase, and other downstream events (1). We modeled the functional selectivity of aripiprazole at the D₂ receptor and its corresponding signaling pathways. Using pipe cleaners and 3D printers, we made prototypes of the G protein-coupled receptor and associated downstream pathways. Our final model was represented in TinkerCAD software.

Materials & Methods

We used Ultimaker 3 3D printers to create a 3D model of the D₂ dopamine receptor and its corresponding signaling pathways.

- ❖ Completed design-related research.
- ❖ Sketched out preliminary and revised designs.
- ❖ Made prototypes of the D₂ receptor using pipe cleaners, binder clips, and string.
- ❖ Created 3D model using TinkerCAD software.
- ❖ Printed prototype models using Ultimaker 3 3D printers at UNC BeAM Makerspaces.
- ❖ Modified 3D design based on challenges encountered and peer review feedback.
- ❖ We were unable to complete the physical 3D model due to COVID-19.

Model Design



Figure 1. Prototypes of the D2R / GIRK Channel

Discussion | Future Directions

Discussion

The D2 receptor (Fig. 1, 2) was created so that the two g-proteins would connect inside it with magnets. We created two buttons that would disconnect one or both g-proteins. When the g-protein disconnects, it swings to the GIRK channel, or a cAMP mechanism (not pictured). The GIRK channel (Fig. 1, 2) was created using a ball and socket mechanism, so the channel would open and close upon the g-protein connecting with it via a magnet. It also includes a spring mechanism that releases a K⁺ ion extracellularly when the channel is opened. The final model would have included a large backboard in which the D2R and the GIRK channel were mounted.

Implications and Future Directions

Our model has implications in both an educational and research/pharmacological setting. It can be used to help students visualize the downstream pathways and functional selectivity to aid in their understanding. In a research and pharmacological setting, our visualization can be used to better understand the mechanism of action of aripiprazole which can be used to gain further insight into the diseases the drug is used to treat. The further intricacies of the functional selectivity and aripiprazole can also be explored. In addition, the activity of ligands for GBy-dependent pathways would be interesting to explore in future directions with this research project. This would present us with insight into potential other pathways involving interactions between the GBy and DRD2 receptor (1).

References

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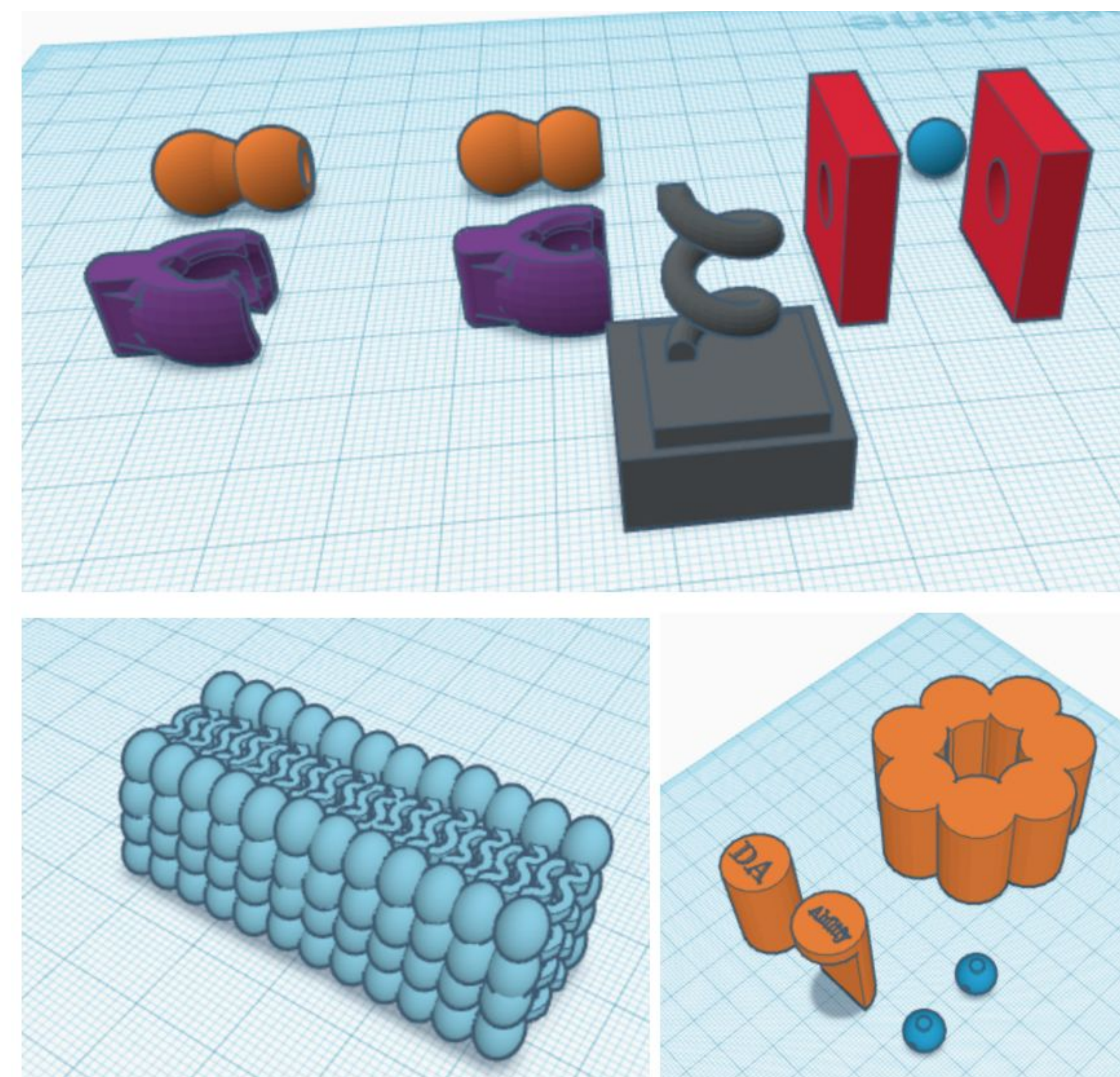


Figure 2. Final 3D Model in TinkerCAD