Designing an Oral Drug for SARS-CoV-2

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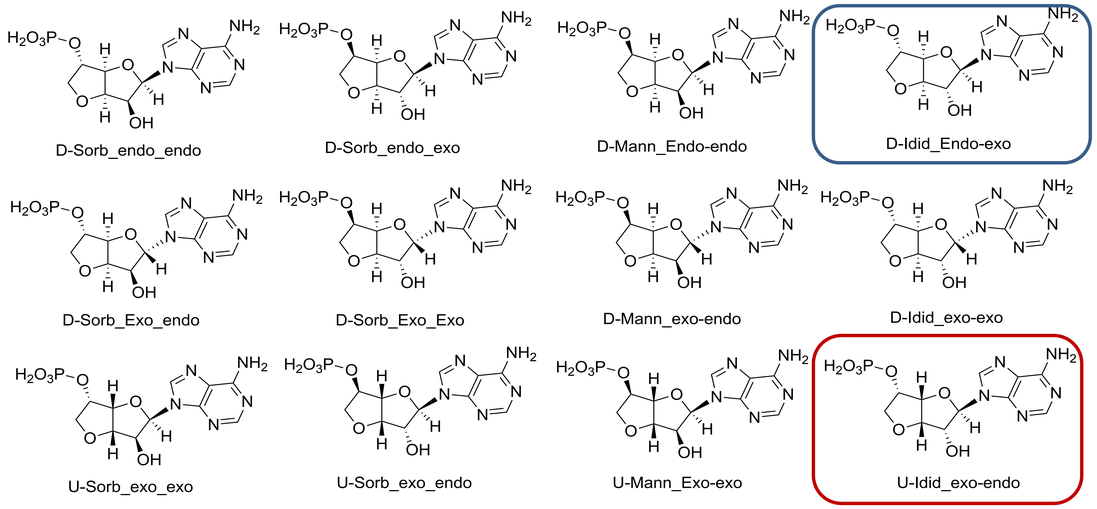
Previous Covid-19 Treatments

Remdesivir was tested in May 2020 as a drug treatment for hospitalized adults who were severely ill with SARS-CoV-2 because it prevents the virus from multiplying in the body, specifically by inhibiting RNA polymerase in vitro. Having a drug that is widely accessible may reduce the amount of people who become severely ill with covid, which is why it is vital that a drug be developed that can be ingested easily and distributed quickly.

Experimental Objective

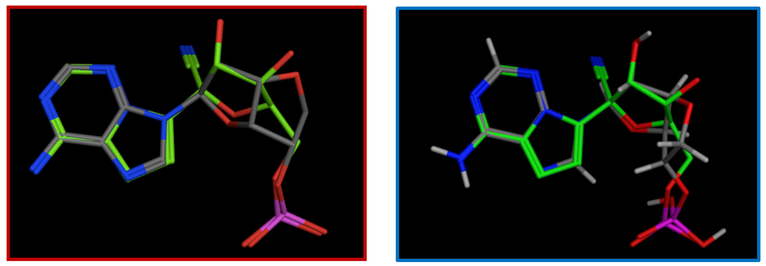
We are trying to develop a drug that is just as effective as remdesivir that can be distributed orally to individuals that are infected with SARS-CoV-2 and possibly prevent the spread of the virus in the pandemic. The objective of this summer's research is to develop a drug similar to remdesivir that can be used to treat SARS-CoV-2 by virtually testing various structural analogues similar to remdesivir in a computational chemistry program MOE to optimize its structure so that it can be synthesized in the lab.

Results and Conclusions



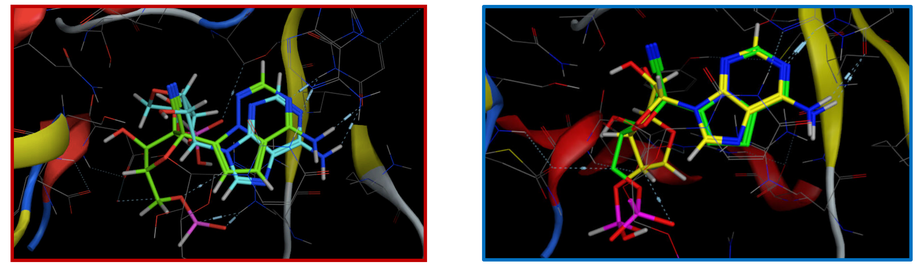
All 12 Unique Isosorbide Analogues.

To target the RNA polymerase that is affected by covid, we examined conformational similarities between isosorbide analogues that shared the same structural backbone and resdesmivir. Structures were sourced from the protein databank while energies and binding mechanisms were simulated using the computational program MOE. The isosorbide analogue that had a cis fused hydrogen bridge, both hydroxyl groups endo to the ring cycle, and adenine exo was identified as the best structural mimic, U-Idid_exo_endo (outlined in red).



Force Field Minimized Overlaps.

The best overlap, U-Idid_exo_endo (outlined in red, structure in grey), was identified and matched with remdesivir's structure (green) as well as the second best overlap, D-Idid_endo_exo (outlined in red, structure in grey).



Docked Overlaps.

Docking simulations were completed in the active site of the protein to identify that although U-Idid_exo_endo (red outlined) had the best structural overlap, D-Idid_endo_exo (blue outlined) behaved most similarly to remdesivir (green) in the RNA dependent polymerase RNA, RdRp.

Future Directions

We propose that better structural overlap may predict biological functions similar to resdesmivir, therefore we will use optimized analogues to guide future lab synthesis. Successful synthesis of the best mimic will be determined in future lab studies by attaining a stable molecule that can be produced in a pill for consumption and functions similar to remdesivir.

Acknowledgments

I would like to thank Mark and Evan for patiently assisting me throughout our computational research, as well as Dr. Spencer Knapp for directing this very meaningful research during this summer. I would also like to thank RISE for funding the I have conducted and introducing me to wonderful cohort of peers and supporters.

References

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