Transforming Growth Factor Beta Receptor I Inhibitor Optimization

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INTRODUCTION

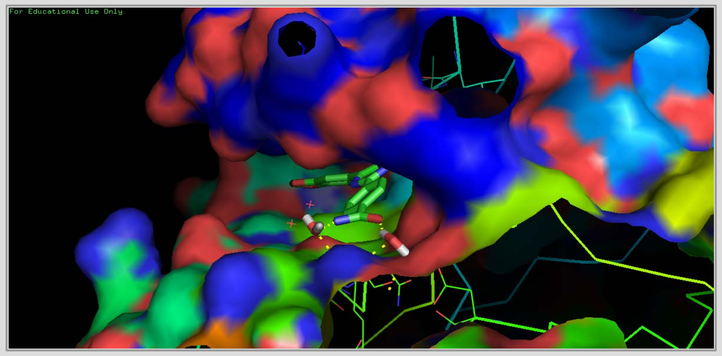
The transforming growth factor beta receptor I (TGF-βRI) plays a key role in regulating cell proliferation and differentiation through signal transduction. Accordingly, many cancers are accompanied by dysregulation in the transforming growth factor beta I (TGF-βI) pathway; in oncogenic cells TGF-βI is often overexpressed. Thus, the suppression of TGF-βRI has shown promise as a targeted cancer therapy. TGF-βI has also been found to play a role in atherosclerosis, marfan syndrome, and loeys-dietz syndrome. Our research aims to optimize TGF-β inhibitors to help treat pathologies resulting from the overexpression of TGF-βI.[1]

To optimize current TGF-βRI inhibitors we considered two factors: binding strength and pharmacokinetics. Through computational chemistry we propose tentative new inhibitor molecules in the results section of this poster.

MATERIALS & METHODS

In order to create the optimal TGF-βRI inhibitor we first analyzed the interaction between GlaxoSmithKline's TGF-βRI inhibitor, SB431542 and TGF-βRI. We obtained the molecular structure of the complex formed between SB431542 and TGF-βRI from the public crystallographic database Protein Data Bank at a 1.7 Å resolution.[2] This complex, called 3TZM, was then viewed on PyMOL, the primary visualization program used in this project. PyMOL is an open source molecular visualization program with some computational chemistry capabilities, such as calculating hydrogen bonds.[3] An example of the molecular visualization enabled by PyMOL can be seen below in Figure 1.

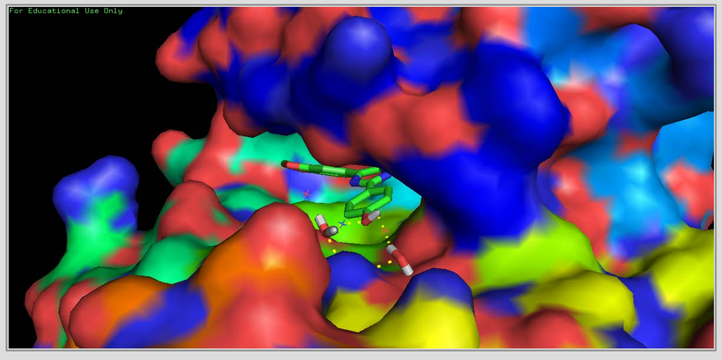
Figure 1: TGF-βRI in Complex with Unmodified SB431542



The dotted yellow lines between the H_2O and SB431542 represent hydrogen bonding and demonstrate the computational chemistry capabilities of PyMOL (Figure 1). In our research, we designed changes in the ligand and visualized the results in PyMOL which allowed us to update interactions. This functionality was used to determine the strength of our inhibitor's fit to TGF-βRI. Through such changes to our model antagonist (SB431542) and computational analysis in PyMOL, we were able to create several candidate molecules with potential for TGF-βRI inhibition.

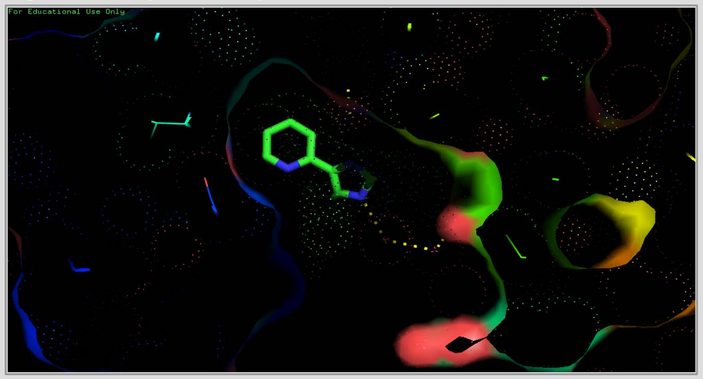
RESULTS

Figure 2: TGF-βRI in Complex with Modified SB431542 (Hydroxyl Replacement of Amide)



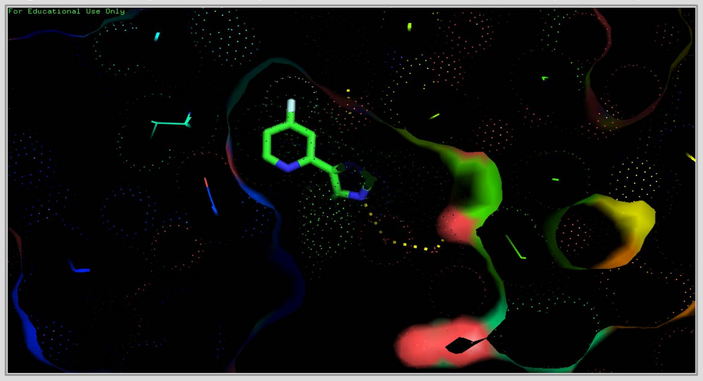
We first set out to design an antagonist with a functional group replacement. By replacing the amide on SB431542 with a hydroxyl, we preserved two hydrogen bonds so binding affinity was preserved; however, overall molecule behavior might be changed. In addition, we propose that the adding of a halogen will prevent metabolic oxidation of the pyridine.

Figure 3: TGF-βRI in Complex with Unmodified SB431542



We next explored optimizing the fit between TGF-βRI and SB431542. In Figure 3, significant space between TGF-βRI and the pyridine ring of SB431542 is apparent. We found a more fidelitous fit with the addition of a fluorine (Figure 4). The surface of TGF-βRI is seen as a line while the van der waals radius of fluorine and other atoms are seen as dotted spheres.

Figure 4: TGF-βRI in Complex with Modified SB431542 (Fluorine)



When we replaced the aforementioned fluorine with bromine, the increase in van der Waals radius was too large and it hindered binding (Figure 5).

Figure 5: TGF-βRI in Complex with Modified SB431542 (Bromide)

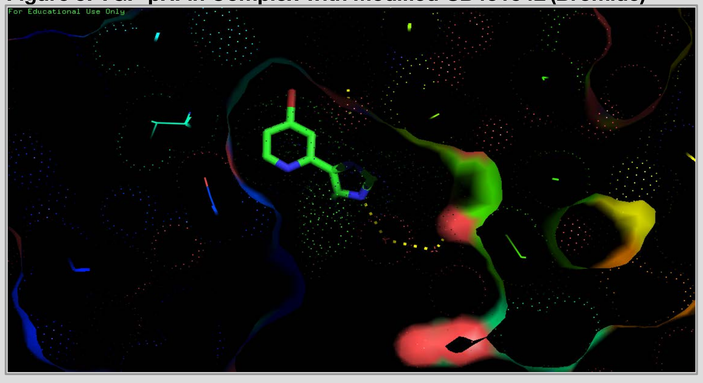
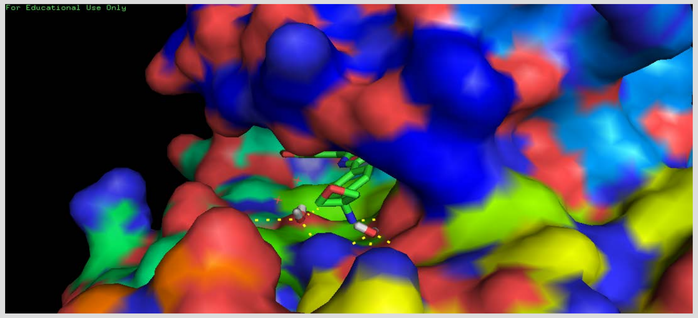


Figure 6: TGF-βRI in Complex with Modified SB431542 (Oxetane)



Finally, we inquired into replacing the oxygen in the amide group with oxetane, which created an isostere for the amide of SB431542. In doing so we found no change in number of hydrogen bonds.

DISCUSSION

In this experiment we proposed three different molecules (Figure 2, Figure 4, Figure 6) that will better antagonize TGF-β according to our computational chemistry. Of these three proposed antagonists, we believe that suggested molecule in Figure 2 will be least effective. The replacing of the amide group with a hydroxyl group maintains bond strength while decreasing molecular mass. In the liver, UDP-glucuronic acid targets hydroxyl groups in a process called glucuronidation, which ultimately results in the excretion of the hydroxyl containing molecules. We believe that the molecule in Figure 6 will be metabolized less than the parent SB431542. Drugs with amides often undergo a process called hydrolysis, which is a preliminary stage of detoxification in drug metabolism. By replacing the amide in SB431542 with an amide isostere seen in Figure 6, we believe we will improve drug potency. Finally, we expect the molecule in Figure 4 to perform well as it has a superior fit with TGF-βRI. Though molecular weight will increase slightly due to the addition of fluorine, we believe this will prevent metabolism of the pyridine.

CONCLUSION

In this experiment, we used computational chemistry to propose new antagonists that we believe will better inhibit TGF-βRI. Of the three new antagonists discussed, we propose two that demonstrate significant potential. To further this research, these proposed molecules should be synthesized and tested as potent inhibitors of TGF-βRI.

ACKNOWLEDGEMENTS / REFERENCES

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3. Schrödinger. "Www.pymol.org." PyMOL. Schrödinger, n.d. Web. Nov. 2015.