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Investigating the Structure of Potential New Drug to Treat Sickle Cell Anemia through Inhibition of the Polymerization of Hemoglobin S

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Nova Southeastern University Honors Protein Modeling

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- PDB: 6xd9
- PDB: 5e83

Primary Citation:

Source 1

- Abdulmalik, O., Pagare, P.P., Huang, B. *et al.* VZHE-039, a novel antisickling agent that prevents erythrocyte sickling under both hypoxic and anoxic conditions. *Sci Rep* 10, 20277 (2020). https://doi.org/10.1038/s41598-020-77171-2

  https://www.nature.com/articles/s41598-020-77171-2.

Source 2

- Metcalf, Brian, et al. "Discovery of GBT440, an Orally Bioavailable R-State Stabilizer of Sickle Cell Hemoglobin." *ACS Medicinal Chemistry Letters*, vol. 8, no. 3, 2017, pp. 321–326.

  https://pubs.acs.org/doi/10.1021/acsmedchemlett.6b00491

Description:

Sickle cell anemia is a hematologic disorder impacting over 15 million people worldwide. It is caused by a single point mutation in the gene hemoglobin-Betha, where a glu group is replaced by val (GAG --- GTG) in the seventh codon (glu7val) of chromosome 1.While healthy hemoglobin (HbA) carries oxygen through the blood, mutated hemoglobin (HbS) does the same action, but it also goes through polymerization, a chemical process of linking monomers together to form polymer chains. Polymerization is one of the key components that causes HbS cells to be more likely to stick together in clusters when they are in close proximity, thus blocking the blood flow in the human body. Researchers from prior studies have discovered that natural mutations reduce polymerization and the sickling properties of the HbS molecules by blocking the secondary interactions which impacts the stability of the HbS structure. In this study we are comparing the antisickling properties of drugs in varied conditions in order to create a drug that is effective in a O2-independent manner and with a 1:1 stoichiometry for lower dosage purposes.
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We compared the main drugs and their respective structures being GBT-440 and VZHE-039. Voxelotor is the first aromatic aldehyde with antisickling compounds that target the polymerization of Hbs. VZHE-039 binds to Hb in a 2:1 ratio whereas GBT-440 binds with a 1:1 ratio. The drugs are in an R2 conformation and interact in the same binding site of the hemoglobin. The major amino acids it interacts with are: The binding site of the protein are Val 1, Val 73, Asp 75, Met 76, Pro 77, Asn 78, Ser 131, Thr 134**.** GBT-440 and VZHE-039 are both aldehydes that inhibit polymerization and antisickling and vary based on the presence of oxygen. VZHE-39 is effective in both environments with 2.5% oxygen and no oxygen.

This study involves combining the oxygen-independent property of VZHE-039 (yellow) and the 1:1 ratio of GBT-440 (blue) to create a new drug (green) that acts in low and high oxygen environments, with low doses. The specific structures responsible for the distinct actions of VZHE-039 and GBT-440 are shown in the following figures as well as combined in the new drug.

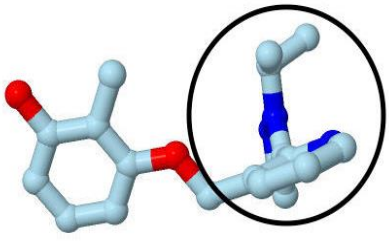

Figure 1: Demonstrates the structure of GBT-440 circling the pyridine and pyrasol structures.

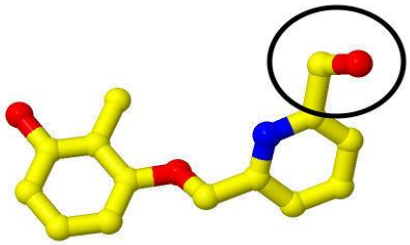

Figure 2: Structure of VZHE-039 and circled methyl hydroxy moite in the pyrimidine ring.

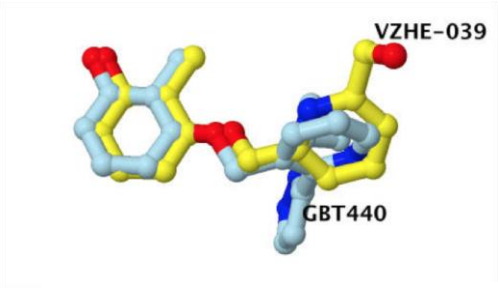

Figure 3: VZHE-039 (yellow) and GBT-440 (blue) represented after both PDB structures were superimposed and only the Hemoglobin S proteins were removed.

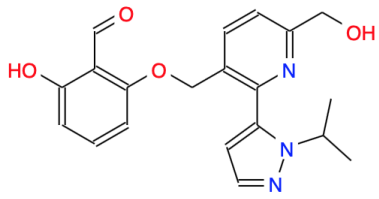

Figure 4**:** New drug structure that consists of the structure of GBT-440 and an addition of methyl hydroxy moite in the pyrimidine ring.

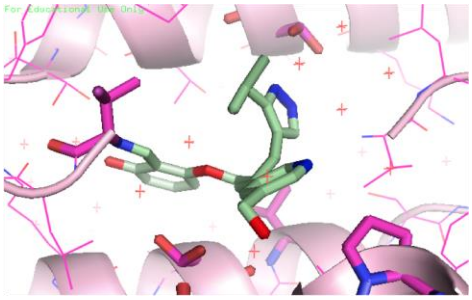

Figure 5: Shows the predicted binding pose of the new drug (green).