UNLOCKING THE BINDING AND REACTION MECHANISM OF HYDROXYUREA SUBSTRATES AS BIOLOGICAL NITRIC OXIDE DONORS.

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Hydroxyurea is the only FDA approved treatment of sickle cell disease. It is believed the primary mechanism of action is associated with the pharmacological elevation of nitric oxide in the blood; however, the exact details of this are still unclear. In the current work, we investigate the atomic level details of this process using a combination of flexible-ligand / flexible-receptor virtual screening coupled with energetic analysis that decomposes interaction energies. Utilizing these methods we were able to elucidate the previously unknown substrate binding modes of a series of hydroxyurea analogs to hemoglobin and the concomitant structural changes of the enzyme. We identify a backbone carbonyl that forms a hydrogen bond with bound substrates. Our results are consistent with kinetic and EPR of hydroxyurea-hemoglobin reactions and a full mechanism is proposed that offers new insights into possibly improving substrate binding and/or reactivity.