# Locking the SUMO Switch: Design of Small Molecules to Inhibit Rhes SUMOylation Sites for Huntington's Disease

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Huntington's disease (HD) is a terrible neurodegenerative disorder, claiming the lives of 2.27 million people annually. HD is caused by an increase in the soluble and mutant forms of the huntingtin protein (mHtt). SUMOylation of mHtt by Rhes (ras homolog enriched in striatum) through the E3 ligase domain triggers the solubility and toxicity of mHtt. Inhibition of the cysteine 263 residue will prevent the formation of tunneling nanotubes further preventing mHtt spread. A model of Rhes and mHtt was constructed using constrained docking. Anchor residues in the protein complex were identified using the web server PocketQuery, which was used to construct small-molecule inhibitors using the web server LEA3D. In order to predict the activity of the inhibitors, a QSAR model was constructed using open-access data on E3 ligase inhibitors. Nine inhibitors were constructed (including cysteine 263). Calculations for the pKd and Gibbs free energy yielded a critical t-value of -4.42 for Gibbs free energy and a critical t-value of 3.804 for pKd, indicating that the Rhes-mHtt inhibitors are more efficient than the controls. RMSD was calculated for the protein complexes. Residues from the mHtt protein were more unstable than residues from the Rhes protein. Retrosynthetic pathways for the inhibitors were also calculated using IBM RXN, which indicated an average of less than 10 steps for all inhibitors and high confidence. The off-target effects of the inhibitors were also calculated using SwissTargetPrediction, and all of the inhibitors had minimal off-target effects.

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