Ubiquitin C-terminal hydrolase (UCH-L1) is one of the most abundant proteins in the brain, constituting up to 2% of total brain protein. UCH-L1 is normally expressed in neurons and testis. The expression of UCH-L1 was found to correlate with Parkinson disease and also tumor progression. Developing effective inhibitors to selectively inhibit the function of UCH-L1 can pave the path to understanding the molecular mechanism of Parkinson disease. From this research, a set of inhibitors and non-inhibitors screened from previous research was docked using molecular docking methods. It was revealed the specific active site of UCH-L1 the inhibitors bind to as well as an understanding of the type of inhibitors that will be effective. It was found that inhibitors that were docked yielded a higher binding energy than the non-inhibitors bound to the active site. The average binding energy for inhibitors were -7.91 kcal/mol and for non-inhibitors were -7.27 kcal/mol. When examining the geometry and interaction of inhibitors and non-inhibitors, it was determined that the biggest effect that contributes to a stronger binding affinity is π-π interaction and hydrophobic interaction.

Methods

The docking study was conducted using the online software SwissDock. SwissDock is a program that predicts the molecular interactions that may occur between a target protein and a small molecule. Within SwissDock, the docking tool EADock DSS is composed of algorithms consisting many binding modes that are generated either in a box (local docking) or in the vicinity of all target cavities (blind docking). The CHARMM energies are simultaneously estimated on a grid and the binding modes with the most favorable energies are evaluated with FACTS, and clusters. The protein files were obtained from the Protein Data Bank for UCH-L1 protein (2ETL). The geometry of UCH-L1 was frozen, and the ligand (inhibitor) atoms were allowed to be flexible within 5Å of a distance.

Conclusions

After the molecular docking of the inhibitors and non-inhibitors on UCH-L1 protein, the molecular interaction that labels compounds “inhibitors” and “non-inhibitors” were analyzed. The inhibitors in the study yielded a higher binding free energy than the non-inhibitors, which is consistent with the experimental findings in experiments. When examining the components that creates such high binding free energy, it was determined that the π–π interactions and hydrophobic interactions play a crucial role. The inhibitors had a higher van der Waals interaction energy than the non-inhibitors. With this knowledge, two new inhibitors were proposed. To increase the VdW energy, electron donor groups were placed on the aromatic ring of the inhibitor. The docking results showed that the proposed inhibitors indeed exhibited a higher binding energy (as well as a higher van der Waals interaction energy as expected). Our study on the interactions between UCH-L1 protein and inhibitor ligands provided the new insights at the molecular level for designing better inhibitors. Our proposed inhibitors will lead to new paths to explore the molecular origins of Parkinson disease.