Substitution Group Effect on the Inhibition of Ubiquitin C-Terminal Hydrolases for Parkinson's Disease Study: Synthesis and Computational Analysis

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Abstract

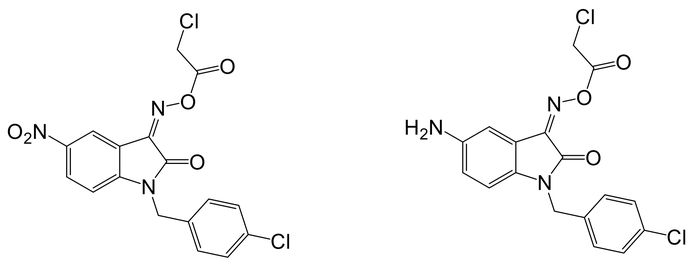
Parkinson's disease is a neurodegenerative disorder that deteriorates motor function which can result in symptoms including tremor, stiffness, and impaired balance. A protein, Ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) has been found to be related to the pathogen of Parkinson's disease and tumor progression. There have been novel inhibitors proposed that was theoretically computed to have a higher binding interaction to UCHL1. Here, we try to synthesize these inhibitors as well as computationally determining if there is indeed a substituent group effect affecting the binding between an inhibitor and protein.

Introduction

Ubiquitin C-terminal hydrolase L1 (UCHL1) is one of the most abundant proteins found in the human brain. Expression of UCHL1 has been associated with Parkinson's disease and proliferation of cancer cells. Inhibitors have been proposed but the binding activity has been yet to be understood. Until recently, Jason An (a former SURF student) and Dequan Xiao at University of New Haven identified the binding site and gave insight to the governing interaction between the inhibitor and UCHL1 and proposed possible potent inhibitors that yielded a higher binding interaction than those inhibitors listed in literature. Even though new potent inhibitors with different substituent groups were proposed, they were not yet synthesized to test the inhibition activities in experiments.

In addition, the computational study of analogues with different patterns of substituent groups on the inhibitor can help to further understand the effect of charge distribution on the interaction between inhibitors and UCHL1. The inhibition interactions can be evaluated through Gibbs free energy calculations, which can be computed based on found binding conformations from molecular docking. A molecular dynamic simulation can then be performed to study the influence of molecular dynamics on the binding interaction between inhibitors and UCHL1.

Proposed Inhibitors



1A **1B**

Figure 1. Structures of previously proposed inhibitors by SURF alumni, Jason An.

Synthetic Scheme

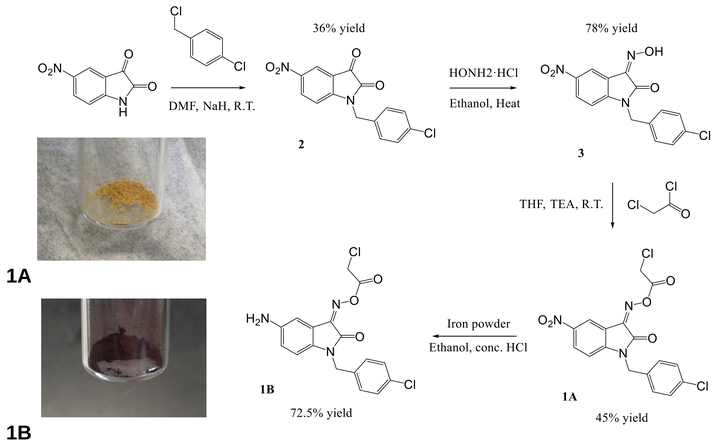
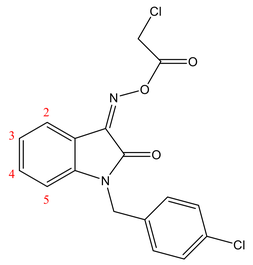


Figure 2. The synthetic scheme proposed for molecule 1A and 1B.

Computational Analysis



Positions	AVG	STD
2monocl	-7.68923	0.373876
3monocl	-7.5571	0.609201
4monocl	-7.38436	0.43918
5monocl	-7.34371	0.468581
2,3dicl	-7.76854	0.479373
2,4dicl	-7.22772	0.509739
2,5dicl	-7.29968	0.559937
3,4dicl	-7.4694	0.349463
3,5dicl	-7.286	2.569191
4,5dicl	-7.23484	0.445083
2,3,4tricl	-7.32398	0.37654
2,3,5tricl	-7.36296	0.564545
2,4,5tricl	-7.24178	0.45924
3,4,5tricl	-7.28959	0.370962
2,3,4,5tetracl	-7.53898	0.197811

Positions	AVG	STD
2monoamine	-7.30709	0.51342
3monoamine	-7.56745	0.356931
4monoamine	-7.34291	0.553167
5monoamine	-7.68136	0.555665
2,3diamine	-7.06718	2.015978
2,4diamine	-7.43649	0.586903
2,5diamine	-7.50362	0.405089
3,4diamine	-7.51763	0.390192
3,5diamine	-7.67826	0.458921
4,5diamine	-7.55366	0.60414
2,3,4triamine	-7.54001	0.336986
2,3,5triamine	-7.41899	1.507972
2,4,5triamine	-7.4721	0.812513
3,4,5triamine	-7.91096	0.349925
2,3,4,5tetraamine	-7.96135	0.298675

Figure 3. Average ΔG and standard deviation for various chlorine and amine analogues. Numbers shown in red represent the position in which a chlorine or amine group is attached (ex. 2,3dicl = chlorine groups attached at positions 2 and 3).

Biological Testing

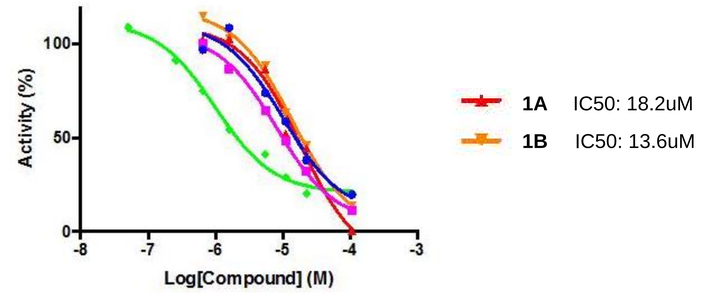


Figure 4. IC50 values obtained by our collaborators at University of Delaware.

Conclusion

We successfully synthesized the previously proposed inhibitors for protein UCHL1 and although these inhibitors are comparable to other known inhibitors and may not be the best, this is a step forward in understanding its interactions. Also, the computational study of the various analogues showed us that there is a substituent group effect that affects the binding between the inhibitor and UCHL1 protein. For example, our general structure regarding the chlorine analogues at positions 2 and 3 yielded a lower delta G or better binding energy while positions 3 and 5 yielded a better binding energy for amine analogues.

References

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Acknowledgements

I would like to give my thanks to Dr. Dequan Xiao for his advisement of this project, Dr. Ho-Yin Lo at the Integrative Materials Discovery Lab for his helpful advice and our collaborators at the University of Delaware. Also, acknowledgement goes to the Department of Chemistry and Chemical Engineering at UNH for the use of their space and instruments as well as the Student Undergraduate Research Fellowship for the funding support to conduct this research.