Synthesis and Physical Organic Evaluation of Rivastigmine Derivatives as Dual Enzyme Inhibitors

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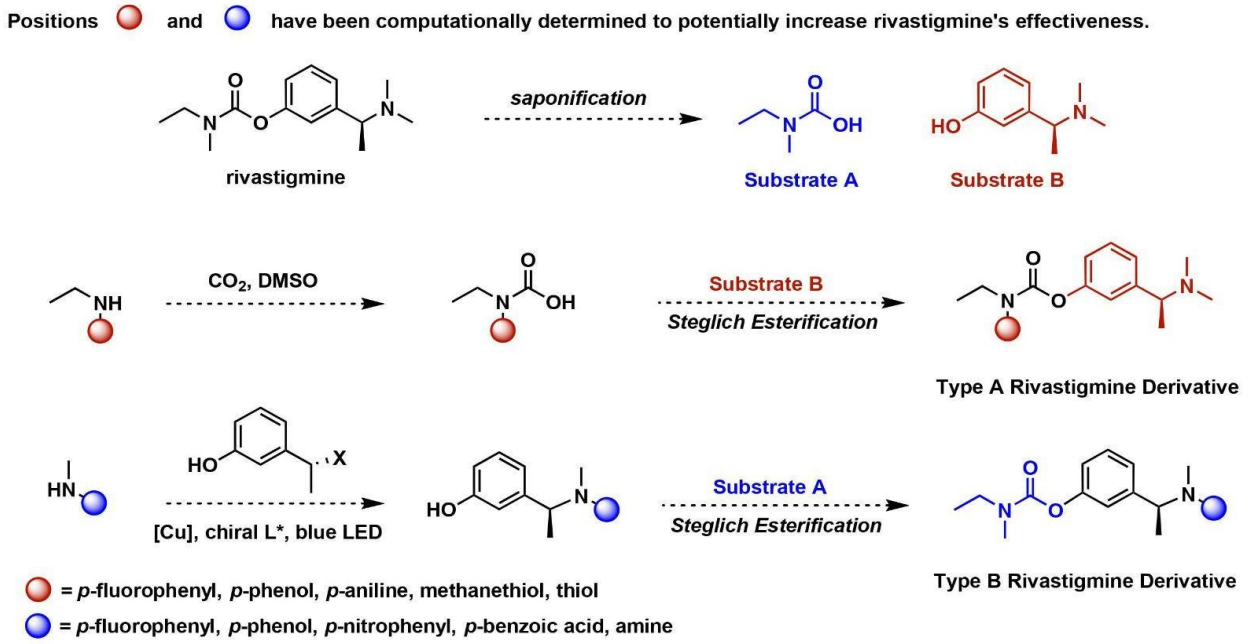
Abstract

Alzheimer's disease is a neurodegenerative disorder affecting millions worldwide. However, current treatments for Alzheimer's are limited and often have side effects. To that end, this physical organic project aims to synthesize rivastigmine derivatives and measure their reactivity with the enzymes they inhibit. The synthesis of ten rivastigmine derivatives identified to be bioactive in a computational study[1] will be designed and executed. The purity and identity of the synthesized compounds will be confirmed using NMR spectroscopy and mass spectrometry. Lastly, a targeted dual structure-activity relationship will be established between the rivastigmine derivatives and their target enzymes (AChE and BuChE) to determine the steric and electronic substituent effects on the rate of enzyme inhibition.

Synthetic Strategy

The general strategy to synthesize these derivatives involves three steps: (1) disconnection of rivastigmine to obtain two key substrates, (2) coupling these substrates with readily prepared starting materials to append the desired substituents, and (3) using Steglich esterification to achieve the final derivatives.

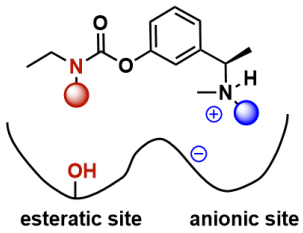


Secondary amines can be carboxylated by bubbling carbon dioxide through DMSO.[2] They can also be cross-coupled with a metal and light catalyst[3] in conjunction with a chiral ligand. Both derivatives can be obtained by performing Steglich esterification on the intermediates and their complimentary substrates.[4]

Intellectual Merit

The proposed project exhibits substantial intellectual merit through its motivation to address Alzheimer's disease and its approach of using accessible physical organic methodologies to probe enzyme kinetics and potential bioactivity. This endeavor aims to take advantage of modern organic synthetic methods to synthesize and investigate the reactivity of rivastigmine derivatives, which have the potential to offer a fresh perspective in a field marked by limited treatment options. Modern organic spectroscopic methods, including 1D and 2D (COSY, NOESY) H-NMR spectroscopy, as well as mass spectrometry, will confirm the structure and purity of the products. In addition, the saponification of the unmodified target molecule to obtain chiral substrates is a unique approach that will make the synthesis of these derivatives more accessible without the usage of a chiral ligand. A unique physical organic-based approach will be explored

to establish a linear free energy relationship (LFER) between the rate of enzyme inhibition for the rivastigmine derivatives and their target enzymes, AChE and BuChE, relative to the rate of inhibition typically seen in rivastigmine.[5] Because the mechanism of action in rivastigmine is based on both sterics and electronics, a Taft and Hammett plot will be established to measure the effects of the substituent size and resonance for the esteratic and anionic sites, respectively.[6] This dual structure-activity relationship (SAR) has the potential to serve as a foundation for further testing on the bioactivity of substituent effects, and could potentially provide broader insight into the molecular mechanisms underlying enzyme inhibition. Lastly, this study serves to confirm or potentially challenge the previous computational calculations of bioactivity.



Broader Impacts

Beyond its intellectual contributions, the project holds considerable broader impacts, the most prominent being its potential to advance healthcare by developing improved treatments for Alzheimer's disease. This project has the potential to provide valuable insights into the design of more potent and selective drug candidates for this debilitating disease. This could impact the healthcare industry by introducing novel therapeutic options and enhancing the quality of life for those affected by this debilitating condition. In addition, this project's alternative physical organic-based approach to enzyme kinetics is one not commonly seen in modern research. The project's approach to testing small molecule bioactivity may have broader implications for the pharmaceutical industry, setting a precedent for the rapid probing of targeted bioactivity using more accessible methodologies. This shift in the drug development paradigm could transform how organic and medicinal chemists approach challenging medical conditions. Lastly, the potential of this research to make substantial advancements in Alzheimer's disease treatment can raise public awareness about the significance of scientific research, showcasing how scientific endeavors can directly impact society's well-being and garnering support for further scientific initiatives. Put simply, this project could provide the foundation for the development of new treatments for Alzheimer's disease that are more effective and have fewer side effects than current treatments.

Conclusion

This project follows a threefold approach: (1) synthesizing two sets of five rivastigmine derivatives that have previously been computationally determined to be bioactive, (2) confirming the identity and purity of the synthesized compounds through NMR spectroscopy and mass spectrometry, and (3) establishing a structure-activity relationship between the rivastigmine derivatives and target enzymes to determine the substituent effects on the rate of enzyme inhibition. This project uses a unique, alternative approach to measuring enzyme kinetics using accessible physical organic methodology and has the potential to act as a foundation for the development of novel treatments for Alzheimer's disease.

References

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