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Novel Alzheimer's Disease Drugs and their Target

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Alzheimer's disease (AD) affects over 5 million Americans, and the number continues to grow as the population ages such that by 2050 the number of Alzheimer's patients may triple to 15 million. Unfortunately, there are no treatments available to arrest or slow the progression of disease. Through the work outlined in this proposal, we will generate the basis for the development of a new lead compound that will be neuroprotective with respect to AD. The invention is based on the demonstrated ability of the non-steroidal small molecule STX to mimic the effects of estrogen without the carcinogenic side effects of estrogen, as STX does not bind to nuclear receptors. However, the nature of the STX target has been elusive. We therefore propose to synthesize a photo-crosslinkable and clickable derivative of STX to identify the putative receptor. Once the receptor has been identified, it will be fully characterized and expressed in model cells to serve as a high-throughput screening system for identifying additional molecules that interact with the receptor. Further, structure-activity relationship (SAR) data will be utilized to generate new derivatives in an effort to optimize the pharmacological characteristics of STX.