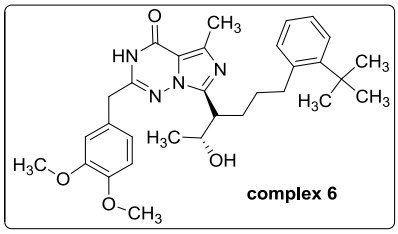
Name:	**Jitendra Kumar**
Supervisor:	**Dr. Nasimul Hoda**
Faculty	**Natural Sciences**
Department:	**Chemistry**
Title:	**Design, Synthesis and Biological Evaluation of Novel Acetylcholinesterase Inhibitors.**

ABSTRACT

Present time, strategy associated with cholinergic hypothesis involves acetylcholinesterase inhibitors which is the main pharmacological approach applied for the treatment of AD. In consideration of these findings and due to the collapse of β-secretase inhibitors at clinical trial acetylcholinesterase inhibitors have re-emerged at the centre of AD drug design. Development and broadening of ligands that attune both amyloid and cholinergic targets. Numerous endeavours have been converged on designing dual binding site inhibitors which halts pro-aggregating activity of peripheral anionic site of acetylcholinesterase and elevating the acetylcholine level in the brain. Dual binding site inhibitors therefore must target concurrently with Trp84 near Catalytic anionic site and Trp279 at Peripheral anionic site for greater potency and tight binding to the enzyme. Among the multiple factors that contribute towards AD progression, Aβ plays significant role in the pathogenesis of AD. The development of drugs which target inhibition of Aβ fibril aggregation is presently a leading approach for the symptomatic treatment of AD. The additional associated hypothesis, namely oxidative stress, occurs early in the progression of AD, resulting from an imbalance between reactive oxygen species production and antioxidant defences leading to the development of amyloid plaques and neurofibrillary tangles formation in brain. Therefore, drugs that target on clearing or preventing the formation of the free radicals in the brain would be beneficial for AD.

The thesis contains five chapters. **First chapter** is introduction describes the origin and causes of neurodegenerative disease and Alzheimer disease (AD) in the world. Various hypotheses that have been established to explain and understand the etiology of AD have also been discussed in this chapter. Natural and synthetic dual acetylcholinesterase inhibitors are used for the treatment of AD have been highlighted. **Chapter 2** deals a series of novel molecules were designed for dual binding site of acetylcholinesterase inhibitors involving triazolopyrimidine and quinolone through alkyne linker. Alkyne linkers plays a crucial role not only in linking but also in enhancing binding potency of ligand to enzyme. **Chapter 3** contains a series of triazolopyrimidine-quinoline and cyanopyridine-quinoline hybrids were designed, synthesized and evaluated as acetylcholinesterase inhibitors. Among them, Ethyl 6-fluoro-4-(4-(5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)piperazin-1-yl)quinoline-3-carboxylate strongly inhibited acetylcholinesterase with IC_{50} value of 42 nM. This compound displayed a composed multitargeted profile with promising inhibition of self-induced and Acetylcholinesterase - induced Aβ aggregation and antioxidant activity. **Chapter 4** reported synthesis and testing of pyrimidine derivatives in conjugation with triazolopyrimidine based hybrid scaffold of acetylcholinesterase inhibitors for development of new molecules towards the treatment of AD. In **Chapter 5,** we designed phosphodiesterase inhibitors by changing the moiety of BAY60-7550 using docking and molecular dynamics simulation. Modification of which gave the extremely selective, high binding affinity of molecule of **complex 6** with PDE2.



complex 6