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Title: Structure based design, synthesis and biological screening of anti-neurodegenerative agents

ABSTRACT

Neurodegenerative diseases (NDs) are the third leading cause of death after cardiovascular diseases and cancer globally. More than 50 million people are reported to have different types of NDs, and the number is foretold to be 152 million by 2050 which is greater than the total population of Bangladesh. The annual cost of NDs is about one trillion US dollar and is also likely to get double by 2030. 4 million people in India suffer from different categories of dementia. NDs are multifactorial disorders and their complete etiology is still unclear. However, some common causes include protein mis-folding, aggregation, inclusion body formation and oxidative stress, neuroinflammation and mitochondrial dysfunction. No medication is available till date that could completely stop the NDs. Some of the available drugs help in increasing the content of neurotransmitters in the brain while some tend to clear the protein misfoldings.

In **chapter 1**, a broad introduction about NDs including their present status, symptoms, causes, available drugs and their success rates were described. Various hypotheses which explain the causes and possible treatments for such diseases were mentioned in detail. This chapter also includes a detailed section describing the recent update in ND therapy (literature review).

In **chapter 2**, some triazine derivatives as potential and selective inhibitors of AChE and BuChE with IC_{50} values in sub micromolar to nano molar range were reported. These derivatives were tested for $A\beta_{1\text{-}42}$ disaggregation, oxidative stress, cytotoxicity, and neuroprotection against $A\beta_{1\text{–}42}$-induced toxicity. These derivatives were found to reduce neuronal death induced by H_2O_2-mediated oxidative stress and $A\beta_{1\text{-}42}$ induced cytotoxicity. One of the best compounds in this series showed $A\beta_{1\text{-}42}$ disaggregation up to 80% which is 1.5-fold better than that of curcumin. Overall, these cyanopyridine-triazine hybrids proved to be potent candidates in Alzheimer's therapy.

In **chapter 3**, one more series of triazine-triazolopyrimidine hybrids was designed, synthesised and evaulauated for anti-Alzheimer effect. One of the best compounds of this group was found to be ~28 fold selective against AChE over BuChE and inhibit $A\beta_{1-42}$ aggregation by 75.5%. These compounds were found to be non-cytotoxic and neuroprotective in nature.

In **chapter 4**, a set of pyrazolo-pyridine carboxylate hybrids (7a-7m) was designed, synthesized and screened for α-Syn inhibition in *C. elegans*. Compounds 7b, 7g and 7i showed computation binding affinity with α-Syn as -6.8, -8.9 and -7.2 kcal/mol, respectively. The test compounds were examined for their α-Syn inhibiting effect on transgenic model of *C. elegans* NL5901 (expressing human α-Syn). The computationally verified lead compounds evidenced to be good in α-Syn aggregation inhibition in *C. elegans.* Overall, the approach of engaging pyrazolo-pyridine hybrids worked with success and these scaffolds could be further modified and corroborated for furtherance of endpoints associated with PD.

In **chapter 5**, a series of traizoles (Tr1–Tr18) was designed and synthesized using azide-alkyne Huisgen cycloaddition reactions. For the *in silico* deign, AutoDock Vina version 1.5.6 was used for flexible docking and redocking. Later, the target molecules were evaluated for *in vitro* inhibition of α-Syn fibrillogenesis and disaggregation. The compounds were also tested for their cytotoxicity effects on A549 cell line. Changes in fluorescence intensities of the compounds upon binding to monomeric and aggregated α-Syn were also evaluated. Some compounds displayed increase in fluorescence when treated with the aggregated α-Syn compared to the monomeric form. Hence, such compounds can be used in cell imaging and can work as florescent dyes for detecting protein aggregation like that of ThT.

In **chapter 6**, diphenyl-1,2,4-triazine hybrids were designed and synthesized using peptide coupling reaction and the synthesized molecules were observed to be persuasive inhibitors of α-Syn fibril formation and disaggregating agents for the treatment of PD. Later, the compounds were tested for their cytotoxicity effects on A549 cell line. Changes in fluorescence intensities of the compounds upon binding to monomeric and aggregated α-Syn were also evaluated. Consistently, compounds A2, A5, A8 and A9 displayed better results in the inhibition of α-Syn fibril formation and disaggregation of aggregated α-Syn.

Overall, five different types of series of compounds were designed, synthesized and evaluated for their ability to act against different NDs in multifunctional ways.