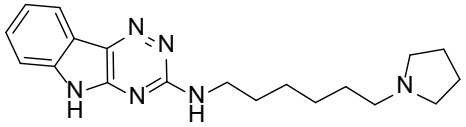
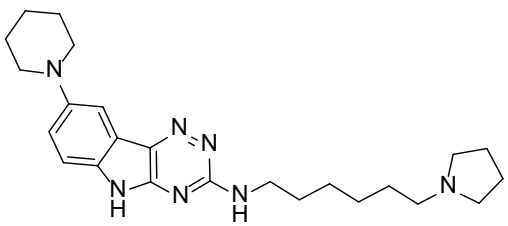
6. CONCLUSION

Considering the multifaceted nature of AD, it was intended to merge two different biologically active moieties, indole and 1,2,4-triazine nucleus into a single scaffold to design a potential anti-AD drug. A combination of the indole ring and the 1,2,4-triazine nucleus by a molecular hybridization approach resulted in a triazinoindole scaffold. Chemical modifications at various positions of the triazinoindole scaffold resulted in a novel series of anti-AD agents. Among them, compound (**199**) was identified as the most active compound with IC_{50} values of 0.56 μM for AChE and 1.17 μM for BuChE (SI value of 2.09). Molecular modeling studies revealed significant interactions between the most potent compound (**199**) with PAS as well as CAS sites of both the enzymes. Results from the docking studies were further validated by time-dependent molecular dynamics study. Compound (**199**) displayed excellent neuroprotective activity against H_2O_2 as well as Aβ-induced toxicity in SH-SY5Y cells in a concentration-dependent manner. Further, it did not show any significant toxicity in neuronal SH-SY5Y cells in the cytotoxicity assay. Compound (**199**) displayed high permeability in the PAMPA-BBB assay. Compound (**199**) was able to significantly reverse the cognitive impairment in both MWM and Y-Maze tests. Restoration of catalase and MDA levels to their normal values supports the antioxidant potential of compound (**199**). Additionally, compound (**199**) is endowed with the capability to restore the memory deficit through increasing glycine levels and decreasing glutamate levels in scopolamine-treated animals. The compound did not show any acute toxicity in rats at a dose of 2000 mg/kg. In addition, it was predicted *in silico* to possess notable ADMET properties. Taken together, all these findings suggest compound (**199**) to be a potential candidate for further development as a novel anti-AD drug.



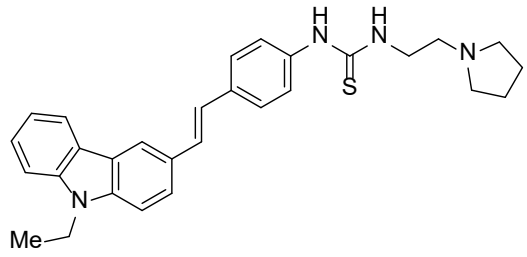
(199)



(261)

Based on the *in silico* metabolic analysis, compound (**199**) was further modified chemically to improve its potency by restricting its metabolism and elimination. Incorporation of various substituents i.e. chloro, bromo, fluoro, methyl, ethyl, and piperidinyl at different positions (C_6-C_9) of the phenyl ring of the triazinoindole scaffold resulted in a novel series of anti-AD agents. Among them, compound (**261**) was identified as the most potent compound exhibiting 1.75-fold and 3.2-fold increase in AChE and BuChE inhibitory activities, (IC_{50} values of 0.56 μM for AChE and 1.17 μM for BuChE) respectively in comparison to compound (**199**). Compound (**261**) demonstrated good antioxidant activity (55.8 % inhibition at 20 μM). Compound (**261**) significantly reversed the cognitive impairment in MWM. Restoration of oxidative stress parameters (MDA and CAT) in the hippocampal region of the rat brain reflects the antioxidant potential of the compound (**261**). Moreover, compound (**261**) did not show any acute toxicity in rats at a dose of 2000 mg/kg, p.o. dose. Based on all these findings, compound (**261**) can be considered as a prime candidate for its further development.

A new series of hybrid carbazole-based stilbene derivatives was designed by the fusion of carbazole ring with stilbene scaffold. All the synthesized carbazole-based stilbene derivatives were evaluated for their anti-AD properties, including cholinesterase inhibitory, $A\beta_{1-42}$ aggregation inhibitory, anti-oxidant and metal chelation activities. Amongst them, compound (**305**) having thiourea linker showed the most promising inhibitory activities against AChE (IC_{50} value of 2.64 μM) and BuChE (IC_{50} value of 1.29 μM). Compound (**305**) showed significant inhibition of self-mediated $A\beta_{1-42}$ aggregation (51.29 % at 25 μM concentration). These hybrids also possessed moderate antioxidant activity. In metal chelation study, compound (**305**) displayed specific metal (Cu^{2+}) chelation property.



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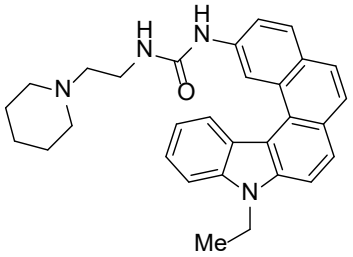

(329)

A series of carbazole-based azahelicene derivatives were also designed by incorporating heterocyclic amines to the designed scaffold using suitable linkers. All the synthesized azahelicene derivatives (**316-329**) were evaluated for their cholinesterase inhibitory and $A\beta_{1-42}$ aggregation inhibitory activities. Among the synthesized compounds, compound (**329**) showed very good inhibitory activities against AChE (IC_{50} value of 1.89 μM) and BuChE (IC_{50} value of 0.54 μM). The selected hybrids (**316-329**) showed good $A\beta_{1-42}$ aggregation inhibition ranging from 53.07 to 67.93 % at 25 μM concentration. Compound (**329**) also displayed specific metal (Cu^{2+}) chelating ability.