6. CONCLUSION

A new series of hybrid molecules combining the benzylpiperidine moiety of donepezil and the diarylthiazole have been synthesized as potential therapeutic agents for the treatment of AD. All the hybrid diarylthiazole-benzylpiperidine derivatives were evaluated *in vitro* for AChE and BuChE inhibition activities. Amongst them, compound **(48)**, exhibited the most promising inhibitory effects towards AChE (IC_{50} = 296±4.0 nM) and BuChE (IC_{50} = 1841.2±29.7 nM). The selected hybrid derivatives **(32, 33, 39, 40, 43, 46-51, 53-56, 74** and **77-79)** exhibited significant inhibition of AChE-induced $A\beta_{1-42}$ aggregation. They further showed noticeable neuroprotective and anti-oxidant activities in the *in vitro* experiments. Compound **(48)** showed ROS scavenging and anti-apoptotic effects against $A\beta_{1-42}$ insult in the primary rat hippocampal neuron cultures. In the $A\beta_{1-42}$-induced Alzheimer's rat model, compound **(48)** improved the spatial learning and memory. Compound **(48)** significantly reversed the $A\beta_{1-42}$ induced enhancement of ChEs levels and positively altered the oxidative stress parameters (MDA and CAT) in the hippocampal region of rat brain similar to the standard drug donepezil. Results of the *in vivo* studies revealed the anti-cholinesterase and anti-oxidant potential of compound **(48)** which further substantiated the *in vitro* findings. Compound **(48)** also exhibited significant neuroprotection in rats subsequent to intra hippocampal injection of $A\beta_{1-42}$ by attenuating the abnormal levels of $A\beta_{1-42}$, *p*-Tau, cleaved-caspase-3 and cleaved-PARP proteins as assessed by Western blot analysis. Moreover, compound **(48)** was found to be nontoxic and well tolerated up to 2000 mg/kg, p.o. dose. Altogether, the beneficial effects of the novel hybrid diarylthiazole-benzylpiperidine derivatives qualified them as potential drug candidates for the treatment of AD and the most promising multi-target-directed compound **(48)** amongst them could be considered as a potential lead for further development.