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Muscarinic Receptor 1 Agonist Activity of Novel Arecoline Derivatives in Alzheimer's Dementia Models

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The cholinergic deficit in Alzheimer's disease (AD) patient's brain has intensified research efforts to test cholinomimetic approaches for efficacy in AD therapy. Various therapies may be of potential clinical use in AD. Among these are cholinergic agents including muscarinic agonists, acetylcholinesterase inhibitors, and acetylcholine releasing agents. One of the muscarinic agonists tested in AD is arecoline and its bioisosters, which are widely, explored as muscarinic receptor 1 agonist (M1 receptor agonist) in AD research. In this regard, we have synthesized five and six membered heterocyclic ring system attached arecoline basic nucleus (*N*-methyl tetrahydropyridines) at 3rd position. Subsequently the synthesized arecolines derivatives were subjected to *in vitro* muscarinic receptor 1 binding affinity studies using male wistar rat brain synaptosomal membrane (cerebral cortex) and also cell line culture studies and extended this *in vitro* studies to *in vivo* pharmacological evaluation of memory and learning in male wistar rats (Rodent memory evaluation, plus and Y maze studies). Some of our synthesized molecules have shown very potent M1 receptor agonist activity and significantly elevated the basal IP3 levels in vitro and also have decreased beta-amyloid ($Abeta_{40}$ and $Abeta_{42}$) deposition in cell lines culture. These molecules have also shown very good antidementia activity in rat dementia model. Conclusions: Molecules with electron donating group as a substitute, has shown very good affinity towards the M1 receptor in vitro and has also elicited beneficial effects in vivo memory and learning models.