DESIGN, SYNTHESIS OF A NEW CLASS OF ORGANOPHOSPHATE ACETYLCHOLINESTERASE INHIBITORS FOR PHARMACOLOGICAL APPLICATIONS

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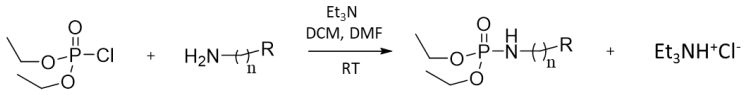
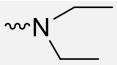
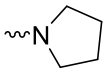
Many organophosphate compounds (OPs) are potent irreversible inhibitors of the enzyme acetylcholinesterase (AChE) that hydrolyzes the neurotransmitter acetylcholine into choline thus terminating neurotransmission. OPs exhibit high toxicity due to acetylcholine accumulation that leads to respiratory failure and are used as insecticides and nerve agents apart from echothiophate applied in the treatment of glaucoma. Their mechanism of action is based on the phospho(r/n)ylation via the reaction of the OP bearing a good leaving group with the catalytic Ser of AChE.

Alzheimer's disease (AD) is a progressive neurodegenerative disease which rises to an epidemiological phenomenon as the elderly population continues to grow. Although various approaches for the treatment of AD have been developed, the use of AChE inhibitors remains the most applicable. Here we attempted to design new organophosphate compounds as cholinesterase inhibitors using a QSAR model, predicting the IC_{50} values in order to expand the OP chemical space for the treatment of AD. Specifically, the leaving group of N-alkyl thiocholines of the V-agents was replaced with N-alkyl aminocholines in order to reduce toxicity. The derived compounds are analogues of the VG nerve agent. The compounds were synthesized through the reaction of diethyl chlorophosphate with various aminocholine derivatives with catalytic amounts of DMF, under Ar atmosphere in the presence of Et_3N with yields ranging from 24,6 to 88,16%.



R	n	Compound
	2	**P1**
	2	**P2**
	3	**P3**
	2	**P4**

The compounds have been characterized by ^{1}H-, ^{13}C-, DEPT-135, ^{31}P-NMR, and 2D (TOCSY) NMR. Then, the stability of the agents was tested in PBS. Further, the *in vitro* biological evaluation is under investigation.