O-Aryl- and O-Alkyldiarylphosphinates. Synthesis and Interaction with Hen Brain Neuropathy Target Esterase and Acethylcholinesterase.

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Phosphinates are one of types of acylating inhibitors of Neuropathy Target Esterase (NTE) which could protect against organophosphate induced delayed neurotoxicity (OPIDN) *in vivo*. They can produce phosphorylated NTE which is structurally incapable of conversion to dealkylated, aged, enzyme. The presence of phenyl group in a phosphoryl moiety of OP molecule is known to lead to increasing its selectivity for NTE in comparison with acethylcholinesterase (AChE).

Two series of diarylphosphinates were synthesized: O-aryl-diarylphosphinates $Ar_2P(O)OC_6H_4$-X (I, Ar = Ph, 4-Tol; X = H, 4-CH_3, 4-NO_2, 4-Br) and O-alkyl-diarylphosphinates $Ar_2P(O)OAlk$ (II, Ar = Ph, 4-Tol; Alk = C_2H_5, C_4H_9, C_8H_{17}). Compounds were synthesized by interaction of equimolal amounts of diarylphosphinic chlorides and pyridine with phenoles X-C_6H_4OH (I) or with correspondent alkyl alcohol (II) in benzene. The products were purified by recrystallization or by column chromatography on Silicagel L100/160.

In vitro inhibitor potency of diarylphosphinates (I) and (II) to hen brain NTE and AChE has been studied. Compounds (II) were shown to be reversible inhibitors of NTE and AChE. Their inhibitor activity to NTE was higher than to AChE and increased with increasing of hydrophobicity of O-alkyl radical: Et < Bu < Oct. O-Aryl-diarylphosphinates (I) were shown to inhibit irreversibly NTE and AChE. Diphenylphosphonates (I) were more potent inhibitors of NTE than corresponding di-4-tolyl derivatives (I). Anti-NTE activity (I) increased with increasing the electronegativity of X: 4-CH_3 < H < 4-Br < 4-NO_2. The studied O-aryl-diarylphosphinates (I) as a whole were rather weak or intermediate irreversible inhibitors of NTE: k_i = 9.0 ÷ 5.3.$10^3 M^{-1}$ min^{-1}. Whereas they have negligible anti-AChE activity (k_i < 10 M^{-1} min^{-1}). These findings suggest that the most potent from NTE inhibitors (I) can be considered as possible protective agents against OPIDN.

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