HTS of Acetylcholinesterase Inhibition

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Acetylcholinesterase(AChE) is a serine hydrolase that belongs to the esterase family within higher eukaryotes. This family acts on different types of carboxylic esters. AChE's biological role is the termination of impulse transmissions at cholinergic synapses within the nervous system by rapid hydrolysis of the neurotransmitter, acetylcholine.

The high-throughput screening (HTS) method was developed in 96-well microplate reaction system using housefly AChE for the search of noble chemical structures without organophosphorus and carbamate skeletons to develop a new insecticide. Several chemical compounds with known mode of action were evaluated by this method, and the inhibitory pattern was analyzed.

Eserine, a carbamate compound extracted from calabar bean was the most potent inhibitor among 17 compounds with I_{50} value of 0.02 uM. Most organophosphorus and carbamate compounds except parathion and acephate showed inhibitory effect. The other compounds not related with AChE inhibition showed no significant inhibition of housefly AChE.

Tacrine, an acridine compound used for the treatment of Altzheimer's disease showed remarkable inhibitory effect on housefly AChE with I_{50} value of 0.27 uM which was just 11.6-fold greater than eserine. It implies that this HTS method using housefly AChE might be used for the discovery of AChE inhibitors because of the low specificity of inhibition between vertebrate and invertebrate AChE.

HTS using housefly AChE was performed against the chemical stock of Korean Chemical Bank in KRICT. Total of 32,160 compounds were screened through 96-well microplate reaction, and 28 compounds were selected with more than 90% inhibition of AChE activity at the range of 12.1 - 54.6 uM depending upon the stock concentration of each compound. Among them, 14 compounds were evaluated to have potent AChE inhibitory effects after determining I_{50} values.

Additional research is needed to characterize the inhibitory properties of each compound, and also the analysis of inhibition kinetics with AChE between insects and vertebrates would be critical for the further development of these compounds.