THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

In Silico Identification Of Potential Oxime Antidotes To Organophosphate Poisoning Based On A Platform Of Novel Therapeutic Substituted Phenoxyalkyl Pyridinium Oximes

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Organophosphates (OPs) are potent and persistent inhibitors of the critical nervous system enzyme acetylcholinesterase (AChE), and many OPs are highly acutely toxic. Prolonged brain AChE inhibition can lead to persistent seizures that can result in brain damage. The currently FDA-approved therapy for OP anticholinesterase poisoning is administration of the muscarinic receptor antagonist atropine (primarily to maintain breathing) and the oxime AChE reactivator 2-PAM (to restore catalytic activity to the inhibited AChE). However, 2-PAM does not appreciably cross the blood-brain barrier and therefore is incapable of protecting the brain from damage induced by high level OP poisoning. A platform of novel substituted phenoxyalkyl pyridinium oximes was invented with the objective of finding an oxime that could penetrate into the brain, restore brain AChE activity following high level OP poisoning, and protect the brain. Our most effective oximes in the platform have shown in vitro efficacy in reactivation of rat, guinea pig, and human AChE that has been inhibited by several potent OPs. These oximes, in combination with atropine, also provide 24-hour survival when rats are challenged with a lethal dose of a highly neurotoxic OP. Our most effective oxime, termed Oxime 20, reduced the time to cessation of seizure-like behavior in lethal level challenge and to providing protection of brain histology in rats treated with high dosages of potent OPs. 2-PAM does not provide this protection. Oxime 20 has been quantified in the rat brain at higher levels than in the blood stream. Oxime 20 also has demonstrated a long half-life in the plasma of rats (10.9 and 12.2 hours, male and female, respectively) and minipigs (7.7 and 22.3 hours, male and female, respectively); 2-PAM half-life is less than 1 hour, based on the literature. Therefore, there is functional and pharmacokinetic evidence that Oxime 20 has the ability to promote survival of potent OP poisoning, to cross the blood-brain barrier, to provide neuroprotection, and to remain in the blood for an appreciable period of time. Using the potency information of 84 oximes in our platform for reactivation of AChE, along with information in a published database on blood-brain barrier penetrability, and using a constraint on the length of the linker chain (3, 4, or 5 carbons only) which connects the phenoxyalkyl moiety to the pyridinium ring, a virtual library of candidate structures was developed which was then computationally screened for likely blood-brain barrier penetrability. Lastly the potential ease of synthesis was taken into account. The result is an in silico framework of potential new substituted phenoxyalkyl pyridinium oximes that are neuroprotective in addition to being life saving that display broad spectrum efficacy with several OP chemistries. The impact of such a new oxime, alone or in combination with 2-PAM, to the JSTO mission and the Joint Force would be greater protection of the warfighter's life and brain function in the event of a chemical warfare attack than is currently possible with 2-PAM alone. (Initial support: DTRA 1.E0056_08_AHB_C; current support: NIH CounterACT U01 NS123255)

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