MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Discovery And Development Of Small Molecule Ache Reactivators

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In 2019 Alchem was awarded “Orthogonal Screening and Development of Small Molecule Cholinesterase Reactivators / Selective M1-M5 Antagonists as Nerve Agent Countermeasures” under 19-05 (TRE) “Prophylactic and Therapeutic cMCM Libraries, Mid to Late Pipeline Development” under OTA W15QKN1691002 to ATI. A primary goal was to discover novel reactivators of organophosphate poisoned acetylcholinesterase (AChE-OP) with improved broad spectrum activity against OP nerve agents vs 2-PAM and HI-6. A combined approach of in silico screening and medicinal chemistry based lead optimization enabled realization of this goal. An in silico compound screening model was first developed based on a sarin AChE-OP X-ray structure. In silico screening of oxime small molecule libraries was performed and “Virtual Hits” ranked by docking score. Over 150 “Virtual Hits” were procured and screened using NIMP based in vitro and rat brain slice ex vivo whole-cell patch clamp AChE-OP assays. Compound AD-83 showed a NIMP assay IC50 of ca. 10 micromolar and was advanced as a lead reactivator for medicinal chemistry optimization. Analogs of AD-83 synthesized over the last year were designed to (1) enhance the reactivity of the oximate anion in the catalytic anionic site (CAS), (2) enhance binding to the peripheral anionic site (PAS), and (3) rigidify the structure to favor the active conformation of the molecule. From this effort a rational structure activity relationship (SAR) for this novel potent class of oxime reactivators has been developed. Superiority to 2-PAM in the primary in vitro NIMP AChE IC50 assay potency screen was achieved with multiple improved analogs e.g. AD-175 in the initial stage of reactivator compound optimization. Testing of improved analogs in the ICD panel demonstrated potency against chemical warfare agents correlating with the NIMP IC50 assay. Aqueous formulation development studies have identified prototypes with high solubility and short-term stability at 25° and 40°C for the compound class. Further optimization has led to AD-255 which demonstrated reactivation NIMP equivalent to HI-6 and broad spectrum reactivator efficacy in the ICD in vitro testing panel. Pharmacokinetic studies of AD-175 and AD-255 in rats demonstrated high plasma exposures consistent with achieving reactivation in vivo, as well as moderate brain concentrations sufficient for AChE reactivation. Intravenous administration of AD-255 and an improved analog AD-260 in a rat AChE reactivation model demonstrated significant efficacy in NIMP suppression of breathing rate. Rat MTD single dose studies up to 100mg/kg showed the compounds to be well tolerated. AD-255 has initiated survival and efficacy testing in the KIKO mouse model, including measuring tissue AChE activity following OP exposure. The program continues to generate improved analogs with AD-260 demonstrating higher potency than HI-6 in NIMP assays. The overall goal to generate a superior reactivator than HI-6 for IND-enabling studies will continue through 2024.

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