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MEETING ABSTRACTS

DESIGN OF BROAD SPECTRUM ANTIDOTES

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The design of reactive molecules such as nerve agent antidotes is inherently challenging due to two intertwined processes imperative for their efficiency: The reversible binding of the initial non-covalent complex in a low energy conformation and the chemical reaction that proceeds *via* a transition state of high(er) energy. Furthermore, a structural and chemical diversity among different nerve agents and their corresponding complex with AChE complicates the design of broad-spectrum antidotes. The development of broad spectrum antidotes has proven challenging and although progress has been made, no new drugs with improved properties have been launched in several decades. Herein, we report a rational, structure-based approach for the development of broad-spectrum antidotes. Based on a hit molecule identified in a high throughput screening targeting the non-inhibited species of AChE, 18 new analogous molecules were designed and synthesized. This resulted in a set of compounds with a diversity in their potency, as desired for subsequent (quantitative) structure-activity relationship ((Q)SAR) modeling. The 18 compounds were investigated for their ability to bind to four different phosphonylated forms of AChE (*i.e.* human AChE inhibited by the nerve agents VX, VR, and tabun, or the substance DFP). The QSAR model was subsequently used to guide the development of a novel set of pyridinium-oxime based broad spectrum antidotes. The mechanism of reactivation of the developed antidotes has been investigated using a combination of X-ray crystallography and molecular modelling.

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