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Synthesis Development And Optimization Of Hlö7 Dms

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Previous methods to synthesize bis-pyridinium organophosphorous nerve agent (OPNA) antidotes like HLö7 DMS required the use of the chemical linkers bis(2-chloromethyl) ether (BCME) or bis(2-methylsulfonoxymethyl) ether (BMME). Not only are these compounds difficult to prepare and are unstable, they are extremely carcinogenic, with an estimated OSHA exposure limit of 0.0003 ppm. The safety concerns combined with the difficulty of synthesis has often made the preparation of these compounds on large scale cost prohibitive.
To solve these problems, Southwest Research Institute® (SwRI®) developed a new chemical technology that avoids the use of BCME or BMME and makes the synthesis of these important antidotes safe and easy to perform on scale. Utilizing the concept of induced reactivity, SwRI designed a bench stable, crystalline linker that is safe to handle and easy to stockpile. In the presence of a Lewis acid, however, the linker transforms into a reactive species that can activate pyridinium oximes to form the bis-pyridinium OPNA antidotes, such as HLö7 DMS.
To produce highly pure HLö7 DMS on scale, however, additional innovations were required. The lack of purification methods for bis-pyridinium OPNA antidotes made achieving purities suitable for animal studies difficult and low yielding. To ensure a reliable process, SwRI also developed two new purification techniques: a preparative ion-pair extraction that can remove bis-pyridinium oxime species out of water and a CaCl2 enabled column chromatography that allows the purification of these oximes on standard silica. Employment of these innovations enabled the synthesis of ~ 300 g of HLö7 DMS with a purity of 95% by HPLC over four discrete operations. The combination of these technologies is expected to enable the further exploration of the chemical space surrounding these difficult to obtain yet promising antidotes.

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