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A calixarene derivative mediates rapid detoxification of the deadly poison VX

On 13th February 2017, the half-brother of the North-Korean dictator Kim Jong-un was poisoned, supposedly with one of the deadliest known chemicals, namely, the nerve agent VX (*O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothioate). This poison is so effective that contamination of the skin with only ca. 10 mg is sufficient to kill an adult. Because of this extraordinary toxicity, VX has been used for the production of chemical weapons, of which massive amounts were stockpiled during the Cold War. Most of these reserves have meanwhile been destroyed according to the regulations of the Chemical Weapons Convention and also the chemicals required for VX synthesis underlie strict control. The murder of Kim Jong-nam is therefore particularly alarming as it shows that VX could be accessible to individuals, including terrorist, planning to commit a crime. In this case, the organization and motives behind the murder and also the source of VX are still unclear.

Fig. 1.

Together with sarin, soman, and others, VX belongs to the class of neurotoxic organophosphonates. These nerve agents act on acetylcholinesterase, an enzyme that plays a pivotal role in signal transduction processes. Reaction of organophosphonates with acetylcholinesterase prevent the enzyme from degrading the neurotransmitter acetylcholine, whose concomitant accumulation leads to severe toxic effects on the central and peripheral nervous system and ultimately to death.

The options to treat poisonings with organophosphonates are, unfortunately, limited. Two strategies are currently in use, usually in combination. Administration of atropine counteracts the effect of the acetylcholine accumulation, whereas certain oximes are used to reactivate the inhibited acetylcholinesterase. Both strategies focus on the symptoms of organophosphate poisonings, whereas a third therapy not yet in use

aims at preventing clinical symptoms altogether by detoxifying the organophosphate before it reaches its target. Certain proteins have, for example, been shown to mediate organophosphate detoxification sufficiently rapidly to allow treatment of respective poisonings. Protein based scavengers have drawbacks, however, rendering synthetic compounds with similar properties attractive alternatives.

Degradation of VX under physiological conditions is particularly difficult because VX is highly persistent. Spontaneous hydrolysis of VX takes weeks in water at pH 7.4, for example. Moreover, degradation of VX requires selective cleavage of the P–S bond because hydrolysis of the P–O bond leads to a product that is similarly toxic as VX itself. That rapid degradation of VX in water at 37 °C and pH 7.4 can nevertheless be achieved demonstrates a recently described calix[4]arene derivative containing a hydroxamic acid-based substituent. Mode of action of this compound involves incorporation of the side chain of VX, which is positively charged at physiological pH, into the cavity of the calixarene ring. The resulting proximity of the VX phosphorus atom and the nucleophilic hydroxamic acid group allows the latter to initiate VX degradation. With a half-life of under 4 min, the calixarene promotes VX detoxification by a factor of 3500 over the rate of spontaneous hydrolysis. Also other V-type nerve agents are detoxified effectively. On the other hand, the action of the calixarene on soman, which lacks the positively charged side chain, is much less pronounced, indicating that the initial complexation step, which is particularly effective if the nerve agent is cationic, is important for rapid degradation.

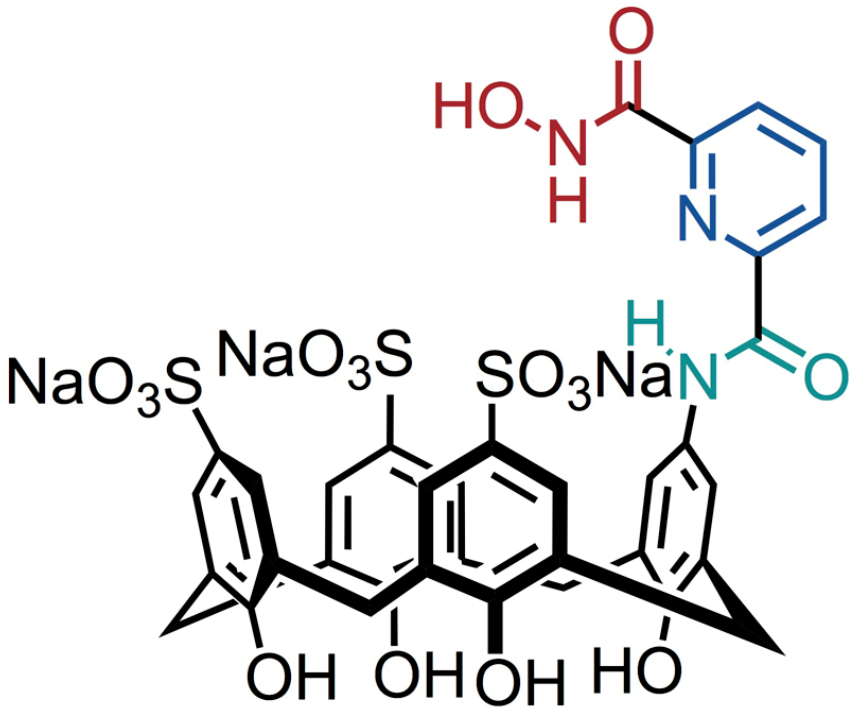

Fig. 2. Structure of the Calixarene-based VX Scavenger.

The calixarene moreover selectively cleaves the P–S bond of VX and complete detoxification requires at least one equivalent, rendering the mode of action stoichiometric rather than catalytic. Although activity is

not yet high enough to allow an in vivo use, this calixarene clearly represents a highly promising lead structure for synthetic scavengers, which may allow in the near future the efficient treatment of victims of organophosphonate poisonings.

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Publication

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