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Supporting information for article:

A conformational change in the peripheral anionic site of *Torpedo californica* acetylcholinesterase induced by a bis-imidazolium oxime

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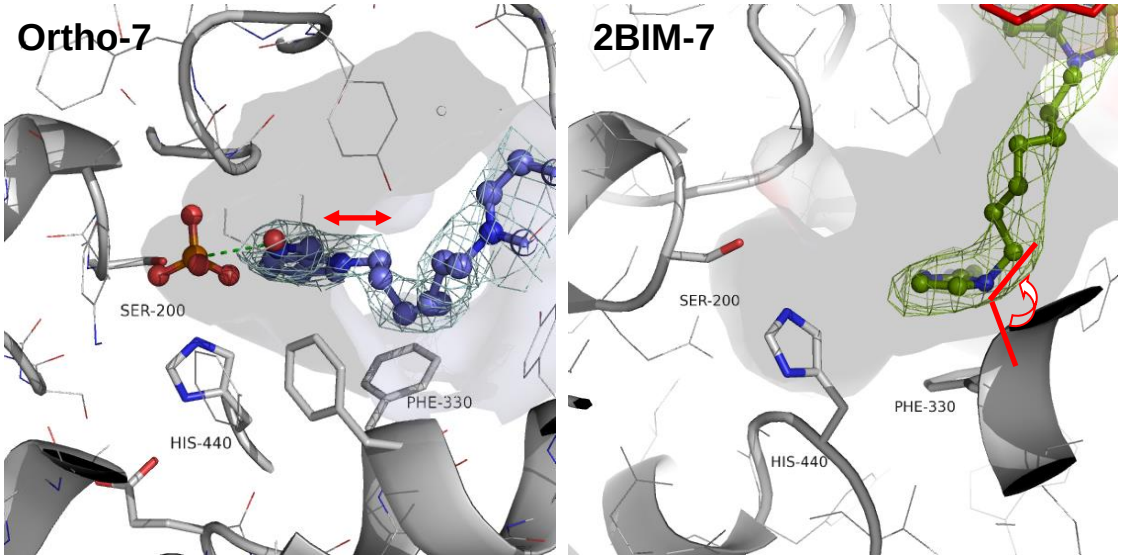
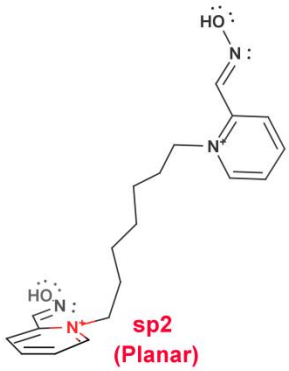
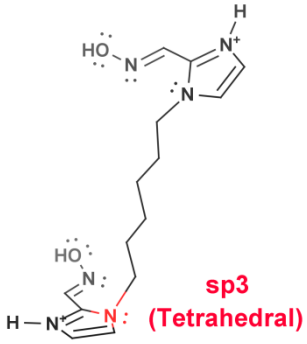
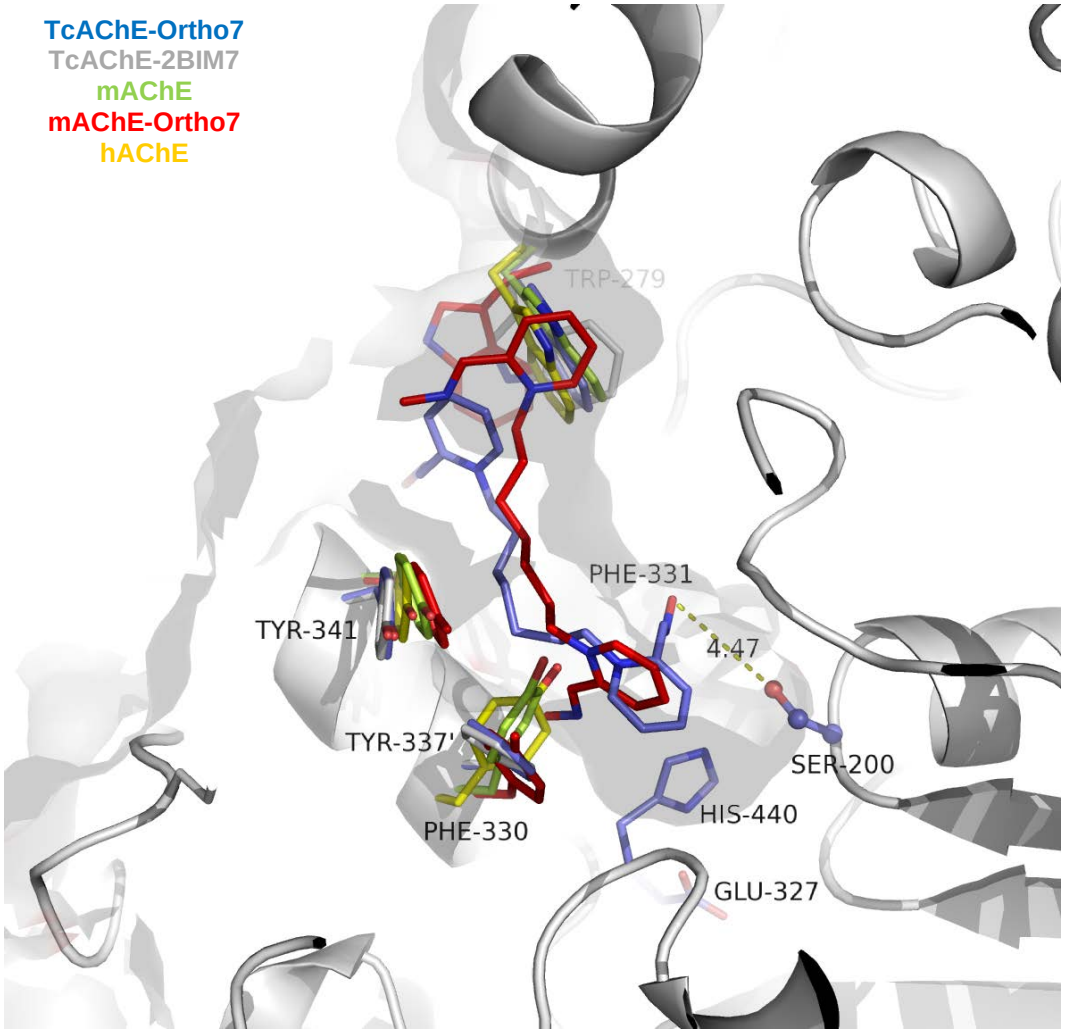
Supplementary Fig. S1 Hybridization of the ring nitrogen of the oxime at the bottom of the gorge. On the left, the first carbon of the linker is in the same plane as the pyridinium oxime, indicating that the nitrogen in the ring is sp2 hybridized (positively charged). On the right, the ring nitrogen attached to the linker is tetrahedral (sp3 hybridized).







Supplementary Fig. S2. Overlay of the TcAChE-Ortho7 (PDB 5BWC, slate blue), TcAChE-2BIM7 (PDB 5BWB, gray), mAChE-Ortho7 (PDB 2GYV, red), mAChE (PDB 1J06, lime green) and hAChE (PDB 4PQE, yellow) structures. The gorge residues of TcAChE and mAChE/hAChE differ by one residue (**Phe-330 vs. Tyr-337**, respectively). In TcAChE the conformation of Phe-330 remains the same regardless of the oxime conformation at the bottom of the gorge (i.e. aligned for attack vs. rotated away). In the free enzyme Tyr-337 of mAChE/hAChE points into the gorge. In overlays, this conformer of Tyr-337 would clash with Ortho-7 when it is aligned for attack. OP-inhibited hAChE can be reactivated by Ortho-7 suggesting that Tyr-337, the oxime, or both must undergo a conformational change in order to accommodate the oxime conformer which is aligned for nucleophilic attack.



Supplementary Scheme S1. **Oxime Reactivation**. The organophosphate nerve agent or pesticide (blue) covalently inhibits AChE. The oxime (red) aligns for nucleophilic attack at phosphorus. The phosphylated oxime leaves, and the active site Ser-200 is restored. The R_1 and R_2 groups attached to the phosphorus vary in size and charge and can affect oxime alignment and nucleophilic attack. In the case of tabun, the nerve agent contains a P-N bond, and the enzyme adduct is more difficult to reactivate. Soman adducts undergo 'aging', a process where the R2 group is lost as a carbocation and a negatively charged P-O^- results. After aging, the negatively-charged oxygen attached to the phosphorus makes nucleophilic attack by an oxime unfavourable and reactivation does not occur.